

Correspondence on the Discovery and Original Investigations on Kuru

**Smadel — Gajdusek Correspondence
1955-1958**



Correspondence on the Discovery and
Original Investigations on Kuru

Smadel-Gajdusek Correspondence, 1955-1958

Edited by
D.C. Gajdusek

Study of Child Growth and Development and Disease Patterns
in Primitive Cultures
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

April, 1975

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PREFACE

These letters speak for themselves. They document the discovery and the origins and pursuance of the first year of study of kuru in great detail and should serve to dispel any misconceptions about who did what, and answer many hows, whens, and whys about the early field work and laboratory investigations on kuru.

Sufficient time has elapsed since Dr. Vincent Zigas and I published our first account of kuru to transcribe this correspondence without any deletions. Only minor errors of spelling, grammar and punctuation have been corrected. Errors in observation, interpretation, and judgement stand as they were committed in writing. I trust that the edification they may achieve will pardon any lack of discretion in presenting them.

D. Carleton Gajdusek, M.D.

ACKNOWLEDGEMENT

Above all else, the publication of these letters is a tribute to the late Dr. Joseph E. Smadel who had so much to do with the first year of our kuru investigation and who provided me with the base laboratory at the National Institutes of Health in which we later were able to demonstrate the slow virus etiology of kuru, the first proved slow virus infection of man. These letters are mostly a correspondence between him and me. They reflect, however, the various other persons who contributed extensively or peripherally to the early study of kuru. Dr. Vincent Zigas, with whom I carried out all the first year of study of kuru in the field, writes or is written to but seldom in these letters except when he is co-author with me. We worked closely together for the whole year from the first moment that he told me about kuru. He left to me most of the liaison with colleagues who could support and assist us. It was he, running in and out of Okapa to his hospital and the airstrip at Kainantu, who provided the lifeline of support on which all our studies were based.

Dr. Frank MacFarlane Burnet, Dr. Cyril Curtain, Dr. Gray Anderson, Dr. John Eccles, Dr. Robert Walsh, Dr. Margaret Holmes, Miss Lois Larkin and the late Dr. Roy T. Simmons in Australia had much to do in providing our first laboratory studies. Dr. John Gunther, Dr. Roy Scragg, Dr. A.V.G. Price and Dr. Terry Abbott of Port Moresby were all instrumental in helping us in the pursuit of our investigations. Miss Elizabeth Jackson, Dr. Smadel's collaborator, kept all these records and laboratory specimens sorted and filed at the NIH and supplies moving to us in the field.

ANU	Australian National University
AMSGS	Army Medical Service Graduate School
NEJM	New England Journal of Medicine
NFIP	National Foundation for Infantile Paralysis
NIH	National Institutes of Health
TPNG	Territory of Papua and New Guinea
USDA	United States Department of Agriculture
WNG	West New Guinea
WRAIR	Walter Reed Army Institute of Research

Letters between Dr. Smadel and Dr. Gajdusek are arranged chronologically and numbered. Associated materials such as letters from either author to other individuals, manuscripts, and reports are given the number of the letter to which they apply most directly with an additional alphabetic code, e.g., 2a and 14a. "Enclosures" refers to materials that definitely accompanied letters between the two authors, and "Appendices" include material that, although it has a direct bearing on the subject of the correspondence, was probably not enclosed with any of these letters.

CONTENTS

Correspondence on the Discovery and Original Investigations on Kuru

Smadel - Gajdusek Correspondence, 1955-1958

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
1. J. E. Smadel	D. C. Gajdusek	WRAIR	16 September 1955
2. J. E. Smadel	D. C. Gajdusek	WRAIR	12 December 1955
<i>Appendices:</i>			
2a. J. E. Smadel	T. E. Woodward	AMSGS	20 September 1955
2b. J. E. Smadel	W. B. Fairchild	AMSGS	19 October 1955
3. J. E. Smadel	D. C. Gajdusek	WRAIR	27 December 1955
4. D. C. Gajdusek	J. E. Smadel	WEHIMR	4 January 1956
<i>Enclosure:</i>			
4a. D. C. Gajdusek:	<i>Papers in progress, in press, in draft form, or suggested for the meetings.</i>		
5. J. E. Smadel	D. C. Gajdusek	WRAIR	19 January 1956
<i>Appendix:</i>			
5a. J. E. Smadel	M. Baltazard	WRAIR	6 January 1956
6. J. E. Smadel	D. C. Gajdusek	NIH	6 March 1956
<i>Appendix:</i>			
6a. J. E. Smadel	C. E. Coffey	WRAIR	8 March 1956
7. J. E. Smadel	D. C. Gajdusek	NIH	8 March 1956
8. D. C. Gajdusek	J. E. Smadel	WEHIMR	26 April 1956
9. D. C. Gajdusek	J. E. Smadel	WEHIMR	5 June 1956
10. D. C. Gajdusek	J. E. Smadel	WEHIMR	7 June 1956
11. D. C. Gajdusek	J. E. Smadel	WEHIMR	28 September 1956
12. J. E. Smadel	D. C. Gajdusek	NIH	11 December 1956
13. D. C. Gajdusek	J. E. Smadel	WEHIMR	29 December 1956
14. D. C. Gajdusek	J. E. Smadel	TPNG	15 March 1957
<i>Enclosure:</i>			
14a. D. C. Gajdusek	F. M. Burnet S. G. Anderson I. Wood	TPNG	15 March 1957
15. D. C. Gajdusek	J. E. Smadel	TPNG	20 March 1957
<i>Enclosure:</i>			
15a. D. C. Gajdusek	F. M. Burnet S. G. Anderson I. Wood	TPNG	20 March 1957

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
16. J. E. Smadel	D. C. Gajdusek	NIH	
<i>Enclosures:</i>			
16a. J. E. Smadel	E. A. Hildreth	NIH	28 March 1957
16b. E. A. Hildreth	D. C. Gajdusek	Maloney Clinic	15 February 1957
16c. J. E. Smadel	M. C. Morris	NIH	29 March 1957
17. D. C. Gajdusek	J. E. Smadel	TPNG	3 April 1957
18. J. E. Smadel	D. C. Gajdusek	NIH	9 April 1957
<i>Enclosure:</i>			
18a. J. E. Smadel	T. M. Rivers	NIH	9 April 1957
19. D. C. Gajdusek	J. E. Smadel	TPNG	14 April 1957
<i>Enclosure:</i>			
19a. D. C. Gajdusek	F. M. Burnet	TPNG	
20. J. E. Smadel	D. C. Gajdusek	NIH	22 April 1957
<i>Enclosures:</i>			
20a. J. G. Greenfield:	<i>Recommendations for removal and fixation of the brain</i>		
20b. M. C. Morris	J. E. Smadel	NFIP	23 April 1957
21. J. E. Smadel	D. C. Gajdusek	NIH	1 May 1957
<i>Enclosure:</i>			
21a. P. Bailey:	<i>Protocol for removal and fixing brains under jungle conditions</i>		
22. J. E. Smadel	D. C. Gajdusek	NIH	Mid-May 1957
<i>Enclosures:</i>			
22a. P. Bailey	J. E. Smadel	NIH	7 May 1957
22b. W. K. Engel	P. Bailey	NIH	7 May 1957
23. D. C. Gajdusek	J. E. Smadel	TPNG	c. 22 May 1957
24. D. C. Gajdusek	J. E. Smadel	TPNG	28 May 1957
25. D. C. Gajdusek	J. E. Smadel	TPNG	Late May 1957
26. D. C. Gajdusek	J. E. Smadel	TPNG	
<i>Enclosure:</i>			
26a. D. C. Gajdusek	A. V. G. Price	TPNG	
27. J. E. Smadel	D. C. Gajdusek	NIH	29 May 1957
<i>Enclosures:</i>			
27a. J. E. Smadel	T. M. Rivers	NIH	29 May 1957
27b. T. M. Rivers	J. E. Smadel	NFIP	21 May 1957
28. D. C. Gajdusek	J. E. Smadel	TPNG	30 May 1957
29. D. C. Gajdusek	J. E. Smadel	TPNG	7 June 1957
<i>Enclosure (2 aerogrammes):</i>			
29a. D. C. Gajdusek	F. M. Burnet	TPNG	4 June 1957
	S. G. Anderson		

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
30. J. E. Smadel	D. C. Gajdusek	NIH	25 June 1957
31. D. C. Gajdusek	J. E. Smadel	TPNG	29 June 1957
32. C. G. Baker (for J. E. Smadel)	D. C. Gajdusek	NIH	7 July 1957
<i>Appendices:</i>			
32a. J. E. Smadel	J. Garland	NIH	July 1957
32b. D. C. Gajdusek	Ed. <u>Science</u>	TPNG	17 June 1957
32c. G. DuShane	J. E. Smadel	<u>Science</u>	1 July 1957
32d. G. DuShane	J. E. Smadel	<u>Science</u>	3 July 1957
32e. D. C. Gajdusek, V. Zigas: Kuru: A Localized "Epidemic" of Chronic Progressive Degenerative Disease of the Central Nervous System in Child, Adolescent, and Adult Natives of the Eastern Highlands of Australian New Guinea.			
32f. C. G. Baker	G. DuShane	NIH	5 July 1957
32g. E. Wipf	D. C. Gajdusek	NIH	2 July 1957
33. D. C. Gajdusek	J. E. Smadel	TPNG	8 July 1957
<i>Enclosure:</i>			
33a. D. C. Gajdusek V. Zigas	T. K. Abbott	TPNG	4 July 1957
34. D. C. Gajdusek	J. E. Smadel	TPNG	10 July 1957
35. D. C. Gajdusek	J. E. Smadel	TPNG	25 July 1957
<i>Appendices:</i>			
35a. R. M. Berndt	R. F. R. Scragg	Perth	9 July 1957
35b. C. Julius	R. F. R. Scragg	TPNG	28 February 1957
36. C. G. Baker (for J. E. Smadel)	D. C. Gajdusek	NIH	26 July 1957
37. J. E. Smadel	D. C. Gajdusek	NIH	
<i>Appendices:</i>			
37a. J. Garland	J. E. Smadel	NEJM	12 July 1957
37b. J. E. Smadel	J. Garland	NIH	6 August 1957
38. D. C. Gajdusek	J. E. Smadel	TPNG	6 August 1957
39. J. E. Smadel	D. C. Gajdusek	NIH	13 August 1957
40. J. E. Smadel	D. C. Gajdusek	NIH	16 August 1957
<i>Enclosure:</i>			
40a. I. Klätzo	J. E. Smadel	NIH	15 August 1957
<i>Appendix:</i>			
40b. H. A. Imus	J. E. Smadel	NIH	8 August 1957
41. D. C. Gajdusek	J. E. Smadel	TPNG	16 August 1957

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
42. D. C. Gajdusek	J. E. Smadel	TPNG	25 August 1957
<i>Appendix:</i>			
42a. T. M. Rivers	D. C. Gajdusek	NFIP	5 August 1957
43. J. E. Smadel	D. C. Gajdusek	NIH	30 August 1957
<i>Enclosures:</i>			
43a. H. A. Imus	J. E. Smadel	NIH	26 August 1957
43b. L. T. Kurland	J. E. Smadel	NIH	
<i>Appendices:</i>			
43c. J. E. Smadel	M. Shy	NIH	26 August 1957
43d. J. Garland	J. E. Smadel	NEJM	15 August 1957
43e. J. E. Smadel	T. H. Ingalls	NIH	29 August 1957
44. J. E. Smadel	D. C. Gajdusek	NIH	12 September 1957
<i>Enclosure:</i>			
44a. J. E. Smadel	T. H. Ingalls	NIH	11 September 1957
<i>Appendices:</i>			
44b. I. Klatzo	D. C. Gajdusek	NIH	13 September 1957
44c. J. Barrau	D. C. Gajdusek	USDA	14 September 1957
45. J. E. Smadel	D. C. Gajdusek	NIH	17 September 1957
46. D. C. Gajdusek	J. E. Smadel	TPNG	18 September 1957
47. D. C. Gajdusek	J. E. Smadel	TPNG	19 September 1957
<i>Appendices:</i>			
47a. D. C. Gajdusek	R. M. Winton	TPNG	19 September 1957
47b. D. C. Gajdusek	T. H. Ingalls	TPNG	19 September 1957
48. D. C. Gajdusek	J. E. Smadel	TPNG	21 September 1957
49. D. C. Gajdusek	J. E. Smadel	TPNG	27 September 1957
<i>Enclosures:</i>			
49a. Australian Museum	D. C. Gajdusek		2 September 1957
49b. D. C. Gajdusek	R. T. Simmons	TPNG	22 September 1957
49c. D. C. Gajdusek	T. H. Ingalls	TPNG	25 September 1957
<i>Appendices:</i>			
49d. L. Hamilton	J. E. Smadel	TPNG	15 October 1957
49e. J. E. Smadel	L. Hamilton	NIH	31 October 1957
50. J. E. Smadel	D. C. Gajdusek	NIH	21 October 1957
51. J. E. Smadel	D. C. Gajdusek	NIH	21 October 1957
52. J. E. Smadel	D. C. Gajdusek	NIH	29 October 1957
<i>Enclosures:</i>			
52a. L. T. Kurland	J. E. Smadel	NIH	18 October 1957
52b. E. C. Horning	C. G. Baker	NIH	28 October 1957
<i>Appendix:</i>			
52c. B. G. Schubert	E. C. Horning	Smithsonian	28 October 1957
53. D. C. Gajdusek	J. E. Smadel	TPNG	3 November 1957

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
54. D. C. Gajdusek	J. E. Smadel	TPNG	4 November 1957
<i>Appendices:</i>			
54a. J. C. Eccles	P. Bailey	ANU	5 November 1957
54b. H. N. Robson, S. Sunderland, J. C. Eccles: Report on the Kuru Disease			
55. D. C. Gajdusek	J. E. Smadel	TPNG	7 November 1957
56. J. E. Smadel	D. C. Gajdusek	NIH	7 November 1957
57. D. C. Gajdusek	J. E. Smadel	TPNG	10 November 1957
58. D. C. Gajdusek	J. E. Smadel	TPNG	11 November 1957
59. D. C. Gajdusek	J. E. Smadel	TPNG	14 November 1957
<i>Enclosures:</i>			
59a. D. C. Gajdusek	R. T. Simmons	TPNG	12 November 1957
59b. D. C. Gajdusek	C. Curtain	TPNG	13 November 1957
<i>Appendices:</i>			
59c. D. C. Gajdusek	E. G. Robertson	TPNG	13 November 1957
59d. D. C. Gajdusek	R. M. Winton	TPNG	15 November 1957
60. D. C. Gajdusek	J. E. Smadel	TPNG	16 November 1957
<i>Enclosure:</i>			
60a. D. C. Gajdusek	F. M. Burnet S. G. Anderson	TPNG	16 November 1957
61. D. C. Gajdusek	J. E. Smadel	TPNG	17 November 1957
62. J. E. Smadel	D. C. Gajdusek	NIH	21 November 1957
<i>Enclosures:</i>			
62a. P. Bailey	J. E. Smadel	NIH	12 November 1957
62b. E. G. Robertson	J. G. Greenfield	Melbourne	31 October 1957
62c. E. G. Robertson	R. F. R. Scragg	Melbourne	16 August 1957
63. D. C. Gajdusek	J. E. Smadel	TPNG	24 November 1957
<i>Appendix:</i>			
63a. R. L. Masland	J. E. Smadel	NIH	24 December 1957
64. D. C. Gajdusek	J. E. Smadel	TPNG	28 November 1957
<i>Enclosures:</i>			
64a. A. L. G. Rees	P. J. Southern	Melbourne	17 July 1957
64b. S. G. Anderson	P. J. Southern	WEHIMR	19 July 1957
64c. A. L. G. Rees	P. J. Southern	Melbourne	31 October 1957
64d. P. L. Davis	J. Garland	Paoli, Pa.	20 November 1957
65. D. C. Gajdusek	J. E. Smadel	TPNG	December 1957

<u>From</u>	<u>To</u>	<u>Written at</u>	<u>Date</u>
66. J. E. Smadel	D. C. Gajdusek	NIH	5 December 1957
<i>Appendix:</i>			
66a. R. L. Masland	C. G. Baker	NIH	6 December 1957
67. D. C. Gajdusek	J. E. Smadel	TPNG	7 December 1957
68. D. C. Gajdusek	J. E. Smadel	TPNG	19 December 1957
69. D. C. Gajdusek	J. E. Smadel	TPNG	24 December 1957
<i>Enclosures:</i>			
69a. D. C. Gajdusek	Ed., <u>Klinische</u> <u>Wochenschrift</u>	TPNG	11 December 1957
69b. D. C. Gajdusek, V. Zigas:	<i>Investigation into the Pathogenesis of Kuru</i>		
70. D. C. Gajdusek	J. E. Smadel	TPNG	31 December 1957
<i>Appendix:</i>			
70a. D. C. Gajdusek	E. G. Robertson	TPNG	24 December 1957
71. J. E. Smadel	D. C. Gajdusek	NIH	6 January 1958
<i>Appendix:</i>			
71a. J. E. Smadel	R. L. Masland	NIH	10 January 1958
72. D. C. Gajdusek	J. E. Smadel	TPNG	12 January 1958
73. D. C. Gajdusek	J. E. Smadel	TPNG	24 January 1958
74. D. C. Gajdusek	J. E. Smadel	WNG	28 January 1958
<i>Appendix:</i>			
74a. The Problem of Possible Dietary Deficiency Underlying Kuru			
75. D. C. Gajdusek	J. E. Smadel	Kuala Lumpur	22 February 1958
76. D. C. Gajdusek	J. E. Smadel	Moscow	27 March 1958
<i>Appendix:</i>			
76a. T. H. Work	J. E. Smadel	Poona, India	20 March 1958
77. D. C. Gajdusek	J. E. Smadel	Leningrad	30 March 1958
78. D. C. Gajdusek	J. E. Smadel	Heidelberg	14 April 1958
<i>Appendix:</i>			
78a. J. E. Smadel	R. F. R. Scragg	NIH	3 April 1958
79. D. C. Gajdusek	J. E. Smadel	NIH	25 July 1958
80. D. C. Gajdusek	J. E. Smadel	NIH	25 July 1958
81. D. C. Gajdusek	J. E. Smadel	NIH	15 October 1958
82. D. C. Gajdusek	J. E. Smadel	NIH	4 November 1958

CORRESPONDENCE

(WRAIR)
16 September 1955

Doctor D. Carleton Gajdusek
c/o Doctor M. Baltazard
Institut Pasteur
Teheran, Iran

Dear Carleton,

I was glad to get letter number two of 1955 from Sarajevo.

Your comments on the malodorous situation in Sweden were noted. Since you have been neutral on the other side in this particular fight, I never stressed the mess. I am pleased, however, to see your grasp of the situation and your violent reaction about it.

We will wait and see how the Bolivian papers shape up in draft form. My first reaction to your proposal of four papers is not too enthusiastic. I believe that it might be better to put the whole business into two reports, essentially combining your one and two and your three and four.

While we are very much interested in the RSSE problem in Yugoslavia, please be a little less generous when you talk to our friends in that country. Of course, we would like to have one or perhaps two recent isolates but why saddle us with seven different isolates.

Your comments on plasma cell pneumonia and pneumocystus are most interesting. Perhaps when the present flurry of writing calms down you can prepare a review on this subject for "Pediatrics" much as you did on the EMC problem.

The other day we received, corrected and returned, the galleys of your papers on the Mexican Indians and your editorial on EMC. I have already sent you a copy of the correspondence on the EHF map. The proof for your Korean paper has not yet arrived.

I now get down to the business that lead me to start this letter. The Commission on Rickettsial Infections meets at the School on 4 November. The subject of Q fever is on the agenda for discussion. I would like the group to learn of your data on Q in Iran and Afghanistan. If the report of the meeting is put out in mimeograph form, which I doubt will happen, then the material will appear under your name from the Department of Medicine, University of Maryland. If the meeting is only an informal one, whichever one of us presents the material will see that you get due credit and you will be listed as the presenter on the program. This problem would cause no great concern if we had the data. Where the hell is it, Chum? I can't even find a carbon copy of the original draft of the manuscript on the Middle East in the files. I trust there is a spare copy parked somewhere just in case you break your neck on one of those jeep rides in Iran. Anyhow, please send (I am now reversing the usual process because you usually say please send)

what you have which can be used for a ten minute presentation on the results of your serological survey in the Middle East. Incidentally, I had a letter from Taylor who complimented you highly on the Quarterly Report. He points out that children in Egypt also have high proportion of Q fever antibodies in several districts around Cairo and that the 0-4 age group consistently ran a few percentage points higher for positives than did the 5-19 or 20 plus. The percentage of positives in the 0-4 groups in several areas ran 46, 37 and 33 percent, respectively. The reference for this paper is, R.M. Taylor, Farag Rizk Hassan, Mohamed Abdel Kader and C.P.A. Strome, Q Fever in Egypt as Revealed by the Complement Fixation Test on Human Sera, Vol. 27, No. 4, pp. 129-140, 1952. Incidentally, Taylor apologizes somewhat for having buried the paper in such an obscure journal.

I have been thinking about your suggestion that Doctor Baltazard would welcome a visit by some of our group. I have discussed the possibility with Mason and MacLeod of stopping for a few days at Teheran on the way out or back to Malaya. According to the present plans we shall be in Malaya for a few weeks during January 1956. I broached the subject to Woodward and Goodner about their going with us as far as Teheran, if we go out over the Atlantic, or meeting us in Teheran for a few days visit at the Institut if we come back via the Atlantic. If Doctor Baltazard plans to be there in January you might diplomatically inquire about his interest in such a visit.

Very best and be careful,

Sincerely,

Joseph E. Smadel, M.D.
Chief, Department of Virus
and Rickettsial Diseases

cc: Dr. Woodward

[WRAIR]
12 December 1955

D. Carleton Gajdusek, M.D.
The Walter and Eliza Hall Institute
Sydney Road
Parkville, Victoria
Australia

Dear Carleton:

This is a reverse "please send" letter.

Enclosed is a letter of 27 September from Bergström. Please send information on the title of the book from which rickettsial translations were made. Mary wrote to Dr. Stahl the same day, requesting the same information, but he has not replied.

Also, where the hell is the translation of the Russian Bergey's Manual? I want the exact reference to Crimean and Omsk HF agent. I may be able to work a trade for EEE, WEE and VEE and the two HF's through the Microbiologic Strain Center in Lucerne, Switzerland.

Merry Christmas.

Sincerely,

Joseph E. Smadel, M.D.
Chief, Department of Virus
and Rickettsial Diseases

2a appendix

(AMSGS)

20 September 1955

Dr. Theodore E. Woodward
University Hospital
University of Maryland
Baltimore, Maryland

Dear Ted,

Geoff and I both read Carleton's letter to us dated September 12 and you know about extending his period of employment. Since none of us thought he really expected to do any work in Turkey and Teheran (and since in his usual fashion he neglected to tell us his plans), we were entirely correct in our original decision to discontinue his salary after 30 September. However, in view of his current efforts, which, presumably, will continue for another month, I would suggest and Geoff concurs, that you ask Mr. Coffey to extend Gajdusek's salary through the 31st of October.

Sincerely,

Joseph E. Smadel, M.D.
Chief, Department of Virus
and Rickettsial Diseases

[AMSGS]

19 October 1955

Miss Wilma B. Fairchild, Editor
American Geographical Society
Broadway at 156 Street
New York 32, New York

Dear Miss Fairchild:

Thanks for your letter of the 17th with the accompanying galley of Gajdusek's paper. All in all I think it is in excellent shape. The first several paragraphs contain a number of erased pencil marks which were inserted when we began to check the galley against our last draft of the manuscript. It soon became obvious that your group had carefully edited the text since the preparation of our file material. These changes improved the manuscript particularly for the lay reader.

I have suggested a two word insert in paragraph 2 of galley 8 and a change of date in the last paragraph of galley 12. In the last paragraph of galley 14 I have changed "in this demilitarized zone" to "in this zone of former combat". The Demilitarized Zone is actually a few thousand yards wide and is not resettled. The other point raised in this paragraph about the resettled area extending south to the 38th parallel is correct. The new line of demarcation between North and South Korea now runs from a point a little to the south of the 38th parallel on the West Coast to a point a little north of the 38th parallel on the East Coast.

A reprint order for 500 additional reprints for our use is enclosed.

Sincerely yours,

Joseph E. Smadel, M.D.
Chief, Department of Virus
and Rickettsial Diseases

(WRAIR)

27 December 1955

Doctor D. Carleton Gajdusek
The Walter and Eliza Hall Institute
Sydney Road
Parkville, Victoria, AUSTRALIA

Dear Carleton:

Merry Christmas and a happy New Year.

This is a long overdue letter which will probably be as disjointed and as unsatisfactory as a number of your more recent ones. I think we can best look on it as a preliminary conversation before we get down to business. I just spent several hours with Nancy and Schmidt trying to bring some order out of our chaotic thinking regarding what might be done with your stuff. Frankly, unless I take a couple of months off or one month and a month or two of somebody else's time, I do not see how this material can be put into publishable form. The stuff that you have sent back is so fragmentary that it does not warrant the designation of even a first draft. I am aware that you also are aware of this. The difficulty as I see it is not in your inability to prepare a proper draft, but in the widely scattered locations of the various bits of data. The job is one of coordination of the various pieces and to do this from a distance of 12 to 15,000 miles is damn near impossible.

We are looking into it further and will try to find some path through what now appears an impenetrable situation.

The method of presenting the poliomyelitis data has never quite satisfied me. Your suggested graph is a distinct improvement. Nancy and I worked on a slightly different graph, a copy of which she will send you within the next few days. If you approve of this, we will proceed to summarize the information in charts of a similar nature. Incidentally, the enclosed quarterly report, which also deals with polio antibodies, uses a somewhat different method of tabulating the data than we employed in the June Quarterly Report. May I have your opinion on this modification also.

One of the main problems not already touched on has to do with the large number of small papers which seem to be staring us in the face. I do not know how to solve this problem either, but I am sure that any editor would look askance at the numerous short subjects. Simply for purposes of discussion at this moment, I would suggest the following titles for the Middle East material:

Serological Surveys in Afghanistan, Iran and Turkey.

- I. Poliomyelitis, Mumps and Herpes
- II. Rickettsial and Arthropod Borne Viral Diseases
- III. Leptospirosis, Syphilis, Psittacosis-lymphogranuloma
Venereum Group, Tularemia and Brucellosis

If possible, within the next week or so I shall try to get a piece of a draft of the first paper in the series using the notes which you sent on.

All of these problems are part and parcel of the business of writing manuscripts while the work is hot and where the data, the co-authors and the ancillary information are readily available.

I shall probably be around here until late spring to wind up such affairs as those we have just discussed and to allow time for my successor, who has not yet been designated, to take over. If we do not get these manuscripts off to the editor before I depart, I trust that we will have them in good semi-final drafts that can be completed without too much difficulty.

With very best wishes,

Sincerely yours,

Joseph E. Smadel, M.D.
Chief, Department of Virus and
Rickettsial Diseases

P.S.

Since the above was dictated I received your letter of the 16th concerned with the Omsk Crimea references and the enclosed one with further comments on the papers. Thanks a lot for all of this. In addition, in looking over the correspondence I found another one of your letters which I had mislaid and which has to do with pictures for your German article on hemorrhagic fever. I'll try and take care of that too. Happy New Year.

P.S. again

The time has come to think of abstracts for the spring meetings. These have to be in before mid-January. Among other things, I have been thinking about one which might deal with an extension of the discussion

to interpreting serological surveys for members of the B Group. Jack Schmidt could do this one which would really recapitulate my two minute discussion after our neurotropic papers in New York last spring and use as data for illustration the neurotropic survey in Iran and Afghanistan. The other might contain the polio survey data on peoples from far away places. In this, one might use the younger age groups from Teheran, Akinlou and from the two groups in South America. This would not be startling, but would answer some of the questions raised by Public Health officials in foreign countries. If we go ahead with this, you will of course, be a co-author, but the Immunologists demand that the first author read the paper. Therefore, Schmidt would probably be first on the neurotropic one and Nancy on the polio one. Meyer would probably be included on the polio one because I would expect him to do the spade work in preparing the manuscript.

JES

January 4, 1956

Dear Dr. Smadel,

I thank you for your careful attention to all the writing problems and I know full well how very unsatisfactory the situation is. Let me attempt a summarization.

Enclosed you will find a list of papers which are under way or in press. It differs very little from your suggestions, and although it may seem to amplify the publications needlessly, I do not think it really does that. The last two (papers 9 and 10) are what you suggest for the meetings and what I likewise suggest. Nancy and Jack are first authors, respectively. The only possible difference, is that you may have thought that paper 9 makes papers 1 and 4 unnecessary. I disagree for the following reasons:

Paper 1 is brief and already completely written and includes a good deal more than polio alone. Finally.. destined for Pediatrics as it is, it finds exactly the right place and audience...for the Journal is South American oriented with Spanish summaries of every article and a wide Latin-American circulation. I still urge prompt final draft of paper 1 and prompt submission to Pediatrics since it contains all the Peruvian-Bolivian serological data we are likely to get. Without it we are left with stray data on Mumps, H.S., PLV, EMC, and Rickettsiae which should be at least recorded. With it, all this is taken care of along with polio.

Paper 4 (you already have the draft) is also brief and properly part of the Middle Eastern series. Without it the "series" falls to pieces. It is better to present polio results independently, I believe, than a hodge-podge of Toxo, Lepto, Syph., Bacterial, etc. These latter, together with Mumps and Herpes can easily be included in the introductory first paper of the series.

Then, paper 10 may make paper 6 unnecessary. I do not think so.

Paper 6 should present briefly the prevalence-incidence data. That leaves the huge study of methods, techniques, and the comparison of HAI with Neuts, and of serum-dilution with virus-dilution, neuts, and the cross-recations, etc. for a lengthy theoretical and methodological study. This would be best left to an independent discussion. I suggest paper 10 for that.

Papers 9 and 10 are for the meetings....and their preparation

I leave to you in Washington. Paper 9, however, is largely written in the draft I sent to Nancy last week with long tables summarizing all our department's work (Tarahumara, Middle Eastern, South American along with the rest of the world literature). If she and Meyer can revise and add to it, it will be ready. It would, I now see, overburden either paper 1 or paper 4 and does not belong with either. Ideally, it would be published as a review-editorial as the EMC review in the same issue of Pediatrics in which the South American (Paper 1) study appeared. This I feel sure is the right place for it.

Paper 2 is already with the editors. All that it needs is the photographs. Since the Klinische Wochenschrift appears willing to print Kodachromes (and they would do a first class job!) I think that here is a chance to get some of the EHF photographic material published. If you can select 3 good color and 3-4 good black and white photographs of clinical material I think that they will print at least the black and white, and perhaps the color, instead. I sent them the charts (glossy prints of clinical course and lab data charts such as used in TB Med and Earle's article in Cecil's textbook) which they will redraw into German. If reprints of the Geographical Review article comes in will you ask Mary to mail me 1 copy air-mail along with those from Pediatrics? I may forward the map-data therein to Germany as their guide in preparing "German" maps.

I have found, in my discussions with ethnologists and missionaries, etc. a large region wherein isolated Aborigines dwell. It appears from reliable reports, that measles was totally absent from the region until one person brought it in in 1943 when it then swept through the aboriginal population decimating them, spreading through the bush from one concentrated mission station to the next and striking 100% of the natives (old and young). It then skipped one entire isolated coastal region and mission but moved by ship further up where it again infected everyone and killed many. Since 1943 there has again been no measles among the children. Here, then, is a really measles-free population where Enders' CF and neut techniques should be conclusive (i.e. no antibodies in children under 13 and 100% in those over 13). Furthermore, remaining CF and neut levels would be proof of antibody level persistence such as could not be obtained in regions where measles is sporadic (most of World) for "asymptomatic secondary infection" would always be suggested. Finally, response to vaccine could best be studied in such a populace...and the need for it here would justify this! Do you believe that anyone in the U.S. would be interested enough to finance this epidemiological study?...which would cost very little. Measles is an old text-book classic. Yet, was a similar situation ever really studied? Do you know of any measles-free population in existence (as this may well be, especially the region "skipped" in 1943).

Please again accept my thanks for your attention to all these writing problems. Do you agree with anything as outlined in the accompanying table? If you do, I think that papers 1-6 might all be submitted by the end of January and, if you can see Morris Schaeffer, papers 8 and 7 might be done by mid-February. Paper 9 is well outlined in the draft I sent. Schmidt and Buescher would have to get to paper 10.

May you have a fine Far and Middle Eastern trip. Please send my greetings to all those who are travelling with you and to the groups in Tokyo, Kuala Lumpur, and Teheran.

Sincerely,

D. Carleton Gajdusek

4a enclosure

PAPERS IN PROGRESS, IN PRESS, IN DRAFT FORM,

OR SUGGESTED FOR THE MEETINGS

(D.C. Gajdusek, M.D.)

1. Subject: Bolivian and Peruvian Serum Survey
Title: SPECIFIC SERUM ANTIBODIES TO POLIOMYELITIS AND OTHER VIRUSES AND TO RICKETTSIAE IN CHILDREN DWELLING IN JUNGLE ALONG THE RIO GUAPAY IN BOLIVIA AND THE PERUVIAN AMAZON
Authors: Gajdusek, Rogers, and Bankhead
Contemplated Publication: PEDIATRICS
Data Included: Polio, Herpes, Mumps, PLV, Rickettial, EMC, etc.
State of Preparation:
Work: Finished
Writing: Good first draft in Nancy's hands. Could be submitted in January.
2. Subject: German EHF review
Title: EPIDEMIC HEMORRHAGIC FEVER
Author: Gajdusek
Contemplated Publication: KLINISCHE WOCHENSCHRIFT
Data Included: Review of clinic. and epidem. of EHF and other HFs.
State of Preparation:
Work: Finished
Writing: Already submitted. Await only photographs from you.
3. Subject: Middle Eastern Studies (I) Background and odd serology
Title: EPIDEMIOLOGICAL STUDIES IN THE MIDDLE EAST. I. BACKGROUND FOR A SEROLOGICAL EPIDEMIOLOGY OF AFGHANISTAN, IRAN, AND TURKEY
Authors: Gajdusek, et.al.
Contemplated Publication: Am.J. Trop. Med. Hyg. or ???.
Data Included: Background data essential to entire study plus odd serological data best not presented in separate paper. To include: Mumps, H.S., PLV, Toxo., Lepto, Bacteriae, Syph.
State of Preparation:
Work: Finished
Writing: First draft in your hands for editing. (Summary of serological data for second half of this paper I am now completing)
4. Subject: Polio
Title: II. NEUTRALIZING ANTIBODIES TO THREE TYPES OF ? POLIOMYELITIS VIRUSES IN SEVERAL COMMUNITIES IN AFGHANISTAN, IRAN AND TURKEY
Authors: Pournaki, Rogers, Gajdusek, Bahmanyar
Contemplated Publication: Same issue
Data Included: All Polio data on Middle East. There is plenty for one, nice brief paper.
State of Preparation:
Work: Done
Writing: Completed draft in your and Nancy's hands. Turkish data must be added.

5. Subject: Rickettsiae Includ. Q
Title: III. COMPLEMENT FIXING ANTIBODIES TO RICKETTSIAE IN COMMUNITIES
IN THE MIDDLE EAST--With a Note on Q fever in Infancy
Authors: Gajdusek, Bankhead, Pournaki, Bahmanyar
Contemplated Publication: Same issue
Data Included: All the Q-fever and Rickettsial data.
State of Preparation:
Work: Done
Writing: I am now working on this.
6. Subject: Arthropod-borne viruses
Title: IV. ARTHROPOD BORNE VIRAL DISEASES
Authors: Schmidt, Buescher, Gajdusek, Smadel
Contemplated Publication: Same issue
Data Included: All prevalence-incidence data but not the involved
evaluation of techniques, methods, and scope of sero-
survey. (see paper 10)
State of Preparation:
Work: Mostly done
Writing: I am waiting from Schmidt on this.
7. Subject: URUMA - Epidemic Bolivian Expedition
Title: EPIDEMIC DISEASE OF UNKNOWN ETIOLOGY AMONG OKINAWAN COLONISTS
IN THE BOLIVIAN JUNGLE
I. Epidemiology and Serological Studies
Authors: Schaeffer, Eichenwald, Gajdusek, Smadel
Contemplated Publication: Amer. J. Trop. Med. Hyg. or ??
Data Included: Background, epidemiol. and full serological studies on
epidemic.
State of Preparation:
Work: Finished
Writing: Morris Schaeffer is preparing this. I will go over draft
as soon as I get it.
8. Subject:
Title: II. Isolation and Characterization of Uruma Virus, A New Virus
Causing Human Disease, from blood of one of the Patients
Authors: AMGS and Schaeffer's team
Contemplated Publication: Same issue
Data Included: Full data on isolation and characterization and serolo-
gical relationships of Uruma virus....including comparison
with Rockefeller viruses.
State of Preparation:
Work: ????
Writing: I sent a "first draft" to you and Schmidt.
9. Subject: Review of Polio Seroepidemiology
Title: SUMMARY OF WORLD DATA ON POLIOMYELITIS NEUTRALIZING ANTIBODIES
IN DIFFERENT POPULATIONS
Authors: Rogers, Meyer, Gajdusek
Contemplated Publication: FOR MEETINGS: then appear as "review" in
Pediatrics in same issue as paper 1. (??)
Data Included: All of Tarahumara, S. American, Middle Eastern, Madagascar,
etc. polio data from Department as well as review of world lit.

State of Preparation:

Work: Done, Finished

Writing: I sent full draft of world data summarized to Nancy last week.
If she and Meyer can check this with the data and synthesize
a report this would be best for meeting.

10. Subject: Neutroropic virus sero-survey evaluation. Theoretical and
practical

Title: SEROLOGICAL SURVEY FOR ANTIBODIES TO THE ARTHROPOD BORNE VIRUSES

Authors: Schmidt, Buescher, etc. etc.

Contemplated Publication: FOR MEETINGS: Then to appear (perhaps) as follow-
up to Middle Eastern survey series (nos. 3-6).

Data Included: All that of paper 6 together with the mass of cross-check
data on individual sera (serum dilution vs. virus dilution;
hemagglut. vs. neut., etc. etc.) Also...compare with
Malayan Japanese, et.al. data.

State of Preparation:

Work: Done???

Writing: Leave this to you and Schmidt and Buescher.

Note: I think that Papers 9 and 10 are what you have suggested for the MEETINGS.
They do not replace papers 1 and 4 and 6, since they are comprehensive
and theoretical in scope. Paper 1 is the only real way to get the full
Bolivian data properly presented. Paper 4 (brief and succinct) is
warranted as such. There is little point combining it with 1. Paper
6 might be combined with 10 if you wish. I think it is better to leave
the "philosophical review" independent!!

[WRAIR]
19 January 1956

Doctor D. Carleton Gajdusek
Hall Institute
Royal Melbourne Hospital
Melbourne, Australia

Dear Carleton:

We are closing out the old Maryland contract of Woodward's and making a new one. It is necessary to balance the books of the old contract. According to Mr. Coffey's phone message a few minutes ago, your account is unbalanced in the amount of several hundred bucks. Please send him any necessary vouchers or return any unexpended funds in U.S. dollars.

Nancy and I are working on the Bolivian, Peruvian Serological Survey.

Very best wishes,

Sincerely yours,

Joseph E. Smadel, M.D.
Chief, Department of Virus
and Rickettsial Diseases

5a appendix

[WRAIR]

6 January 1956

Doctor M. Baltazard
Director
Institut Pasteur de l'Iran
Teheran, Iran

Dear Doctor Baltazard:

Very best wishes for the New Year.

It is with great regret that I write you regarding a change in plans which will cause a delay of some months in our visit to Teheran. Doctor Woodward cabled you yesterday about this and he too is writing.

Several unforeseen and unavoidable circumstances caused us to rearrange our plans for this trip some time ago. However, these changes were concerned with the visits at the Army laboratories in Tokyo and Kuala Lumpur and we still expected that all of us would be able to reach Teheran about February 20th and to accept your kind invitation. The fates continued to be against us and now we find it impossible to make the trip.

One of the things we wished to talk to you about was the matter of continuing some of the collaborative studies that your group, Woodward's group and mine began with the visit of Gajdusek. This preliminary effort has already been most productive from our point of view and additional medical data will continue to accumulate as the results become available from laboratory studies which are still in progress here on material that was collected.

One of the deciding factors on our delaying the visit was concerned with loss of certain key personnel and facilities which might have been available to provide the laboratory support here for any future collaborative work by our groups. It is hoped that we may be able in the not too distant future to arrange for such support--which is absolutely vital to successful field-laboratory studies. If this does prove to be feasible then Doctor Woodward will write to you in a few months to see whether he and Doctor Goodner might visit you to discuss such matters.

With very best wishes,

Sincerely yours,

Joseph E. Smadel, M.D.
Director
Division of Communicable Disease

6 March 1956

Doctor Carleton Gajdusek
Hall Institute
Royal Melbourne Hospital
Melbourne, AUSTRALIA

Dear Carleton:

After innumerable delays Jack Schmidt and I have sat down to work over those God-damn papers. I must say that the stuff you have sent would have been just exactly what I was looking for provided that you had given it to me last April as a report to the Surgeon General's Office. As it stands when we attempt to make scientific papers out of the material, it is a mess. The seven or eight double-spaced legal size sheets on the geography of the Middle East would make a welcome edition to any high school text-book on geography, however, chum, we are writing medical papers and not geography.

Having got the above off my chest, we will settle down to the work. In a couple of weeks you can expect to receive a copy of the draft of the first paper. When you go over this do not add the innumerable conversationally interesting points about the travelog aspects of the trip. Furthermore, do not ask for us to include any travelog pictures in this paper, so what if they live in mud houses or holes in the ground. This information may be all right for a sociomedical review of primitive conditions, but we will include it in the scientific papers on infectious diseases only when or if it bears directly on the epidemiology and ecology of a particular disease under discussion. Much of the same line of reasoning goes with the South American papers. I have noticed on the draft that has been returned that you have added a fair amount of travelog information. Remember the old dictum in newspaper writing--if you are in doubt about the pertinence of a paragraph, leave it out.

Burnet spent the day here and we had a pleasant time.

Kindest personal regards,

Sincerely yours,

Joseph E. Smadel, M.D.
Director
Division of Communicable Disease

P.S.

Enclosed are a few pages of the first draft of the manuscript entitled, "Serologic Survey in the Middle East."

6a appendix

WRAIR

8 March 1956

Mr. Charles E. Coffey
Accounting Department
University of Maryland
College Park, Maryland

Dear Mr. Coffey:

Enclosed are receipts for expenditures incurred by Doctor D. Carleton Gajdusek during the work on viral and rickettsial diseases in the Middle East, which was undertaken under Contract DA-49-007-MD-77 (Field Studies on the Control of Infectious Diseases of Military Importance), with Dr. T.E. Woodward as the responsible investigator.

I hope these receipts will balance with the expenditures you have listed for Dr. Gajdusek under Dr. Woodward's contract. If there are discrepancies, please let me know and I will try to solve the problem before I leave the WRAIR in April. Just for your records, Dr. Gajdusek's present address is:

Hall Institute
Royal Melbourne Hospital
Melbourne, Australia

Sincerely yours,

Joseph E. Smadel, M.D.
Director, Division of Communicable
Diseases

8 March 1956

Doctor D. Carleton Gajdusek
Hall Institute
Royal Melbourne Hospital
Melbourne, Australia

Dear Carleton:

I just read your review on Pneumonocystis Carinii. I think it excellent and suggest that you publish it promptly. I have only one question to raise regarding the manuscript. This is toward the bottom of Page 29 where you are discussing APC's and salivary inclusions. There is no reference cited and I am not clear in my own mind about the real validity of inclusions in cultures infected with ARD-APC. Neither am I clear regarding the relation of APC to salivary inclusion disease. Doctor Margaret Smith of Washington University has obtained beautiful inclusions with the human salivary gland agent grown in human cell tissue cultures. All and all, I would re-arrange this portion of the manuscript.

I am showing it to Charlotte Campbell and Tony Morris for their information. If they have other comments they shall transmit them to you.

Sincerely yours,

Joseph E. Smadel, M.D.
Director
Division of Communicable Disease

[WEHIMR]
26 April 1956

Dr. J. Smadel
Director
Communicable Diseases Division
Walter Reed Institute of Research
Walter Reed Army Medical Centre
Washington, U.S.A.

Dear Joe,

I have received the new Russian articles on hemorrhagic fevers and I am most interested in them. Furthermore, the news that you now have both Omsk and Crimean viruses in your hands is most exciting. The Central European-Russian hemorrhagic fever is apparently that which we reviewed in the manuscript as Yaroslavl hemorrhagic fever, as it was referred to in the earlier reports. Even then - as also in the German review now in the press - I have commented on the impression that albuminuria and other renal symptoms are prominent in this variety as in EHF. However, Hungarian hemorrhagic fever has been better documented than this Central European-Russian disease (Yaroslavl) and is accompanied by renal manifestations and pituitary pathology, yet it cannot be accepted unequivocally as Far Eastern EHF on the basis of existing information. It will certainly be interesting, however, to see what the Russians turn up in their serology. Do they have a virus isolated from the Yaroslavl hemorrhagic fever? I have corrected second proofs on the German EHF article. Since they shall publish a large page of the kodachromes, do you not want more reprints?

Omsk HF is clinically a very distinct disease and the current identification with RSSE is most surprising and intriguing. We now have four distinct diseases to attribute to this virus:

- (1) Classical RSSE
- (2) Louping ill
- (3) Omsk hemorrhagic fever
- (4) Diphasic meningo-encephalitis (which is undoubtedly the same as the tick encephalitis of Slovenia, Austria and (?)Czechoslovakia).

I am most interested in the new Russian designation diphasic milk encephalitis for this latter syndrome. If this diversity of clinical manifestations and epidemiology for viruses that are serologically identical is substantiated, we have a most remarkable instance of variation in pathogenicity and, obviously, our extensive reliance on serological classification will no longer stand us in good stead. With Vaccinia - Variola - Alastrim we have much the same situation.

I am obviously very interested in what happens with the Crimean hemorrhagic fever strain. You had best not wait too long before getting it into tissue cultures and volunteers. I plead the use of healthy, sound, and free volunteers, not prisoners or Asiatics.

What did Chumakov have to say on Uzbekistan hemorrhagic fever? Did he claim that they had any virus isolated or have they "lost" it? What about the Russian Type 4 polio which Sir Mac heard about in the U.S.?

In a recent letter to Charlie Wisseman, I told him that later this year I shall be going to New Guinea and New Britain to make a field study of child growth and development among tribal peoples in the area, who have had as little contact with Western civilization as any people in the world. While there I shall naturally make what epidemiological observations I can and I would hope to return with a good serum collection, collected largely from infants and children. There are no proper bleeding venules in Australia. If the Armed Forces Epidemiological Board, your Department or Charlie's dengue project could be used to supply me with an adequate number of the 15 and 30 cc British varieties I should be most grateful. I believe it would be foolish to pass up the opportunity which my work with the natives may provide for getting the sera even if we simply file them away. Somewhere between Malaya and Australia, Jap. B and MVE must meet and a priori I know of no way we could predict which of the two would be present in this critical geographical location. Furthermore, such sera might eventually prove of considerable value in the intensive study of the group B agents including dengue, which Charlie tells me he has now undertaken. Finally, my pediatric interest will dictate extensive collection of specimens from infants and children - and these may be of particular interest in providing some cases with one or few previous exposures to arthropod-borne viruses. I shall carry through a study on Cape York Peninsula - Gulf of Carpentaria - in the now measles-free aboriginal population as soon as I can prepare equipment for this project. I believe I have written to you previously with a prospectus of the study. Enclosed is a revised account of the measles situation in the area. It is unique enough, I believe, to be used as a major test project for Enders' new neutralization and complement fixation antibody tests. Furthermore, if I should get to the region before measles again enters, it is obviously an ideal place to settle the matter as to the duration and titre of both antibodies after infection in the absence of repeated new exposure. For these bleedings I would also need a few hundred venules and this project, unlike that of the islands, is awaiting nothing more but my securing such venules, since air transportation into the region has already been promised me by the Flying Doctor Service. If you can possibly provide me with the venules, particularly if there would be any chance of air shipping enough for this Queensland undertaking - will you let me know?

I am very interested in Charlotte Campbell's comments on the Pneumocystis carinii paper. The matter as to whether the parasite is protozoan or mycotic

is hotly disputed, although many protozoologists in England and on the Continent accept it as a protozoan. Its presence in the lungs and its undoubted role in the pathogenesis of this serious human infection is the important matter and the morphological and taxonomic questions can be settled after the laboratory workers culture an organism. In a series of new reports which I am incorporating into the review, passage of the organism in animals is reported. I am getting - I hope - pathological material from Yugoslavia and will try to get some into your hands. I, myself, believe that in time Pneumocystis carinii will be accepted as a fungus.

In a letter I have just received from George Adams, chief of the Division of Health and Sanitation of the U.S. Operations Mission to Bolivia, he tells me he sent to me via diplomatic pouch to Washington, a comprehensive clinical "Informe" by Doctors Antonio Brown and Silvio Palacios on the Uruma epidemic. I suspect your or Schmidt have this and are using its material in preparing the Uruma papers. I would very much like to see this report, and when Schmidt can get a revised draft of the Uruma virus report off to me, would you please ask him to include this report. I shall return it. I have also heard nothing further about the clinical epidemiological report on Uruma fever, a draft of which Schaeffer was to have sent me. I shall write to him again.

Sincerely,

/s/ Carleton

D. Carleton Gajdusek, M.D.

[WEHIMR]
5th June 1956

Dr. Joseph E. Smadel
Director of Communicable Diseases Division
Army Institute of Research
Walter Reed Army Medical Center
Washington, D.C.

Dear Joe,

I have just received an air shipment of 250 vacuumatic venules in good condition and immediately arrangements for the Northern Queensland - Cape York Peninsula expedition have been started. I shall do my best to get specimens that may be used for dengue, MVE, Jap. B and SLE serology, as well as for the measles antibody study that prompts the investigation. Naturally such sera will be of interest for herpes, Q and other studies also, if I am able to obtain an adequate age distribution. Thank you for your prompt help in getting the venules to me, for they are unavailable here in Australia and only their lack has delayed the venture.

I am also planning to visit New Guinea and New Britain, where my interest in child growth and development in the primitive cultures is the primary incentive. If I can equip myself in time, I shall make a preliminary trip there just after the Cape York Peninsula visit.

I have not seen anything further of the Middle Eastern or the South American papers from the A.M.S.G.S. or from Morris Shaeffer. Will you let me know what the state of the various serological reports from the Middle East and South America now is and what is being done about the Uruma virus report? I am prepared to devote further time to the papers as soon as the revised versions are sent to me. Finally, what papers were given at the spring meeting?

The Pneumocystis carinii paper - much modified, corrected and revised - has been accepted for publication in PEDIATRICS. I shall send the new version of the manuscript to keep on hand for anyone who may be interested in it. Histological material from Yugoslavia is now in my hands and I shall have photomicrographs made. I now find that a Sydney pathologist has now found Pneumocystis carinii forms in the lungs of two child patients and the agent has thus been identified in Australia. The controversy as to whether it is a fungus or not is still unsettled. I should appreciate any comments readers may make on this revised version.

My project here in Melbourne has settled on infectious hepatitis, a problem on which no one here was at work and one made possible by the large two-year-old

epidemic which is still in progress in Victoria. I am searching by numerous techniques for antigen in tissue of acute patients. The old idea of hunting down antigen in acute tissue is more trouble than it is worth in most diseases which can be studied by any other means. In hepatitis, however, we are at an impasse; we know that some antigen is present from the work in human volunteers and the only question is whether we can devise methods sensitive enough to detect it. I have been able to increase the sensitivity to the complement fixation techniques and I am, furthermore, concentrating also on hemagglutination and other methods of antigen detection. Naturally, acute serum specimens are one issue for investigation, but my efforts are concentrating on the liver from sudden death from acute yellow atrophy. Feces may also be worthy of investigation. There is little chance that I can complete this project in my short year here and if it still seems as promising to me late this year as it now does, I shall certainly hope to continue with it when I return to the United States. Thus far I have nothing to report. The German paper page proofs have been corrected and we are now only waiting for the proofs of the Kodachromes. Thank you for your help on this matter also.

I will certainly be able to use more than the 250 bleeding venules I now have, as I indicated in my previous letter, but the time emergency is now solved and should you possibly be able to send others, surface freight would be satisfactory. Please let me know what your new job entails and where I may address you in the future.

I trust that this letter will reach you through the old address.

Sincerely,

/s/ Carleton

D. Carleton Gajdusek, M.D.

P.S. Sir Mac's work on flu filaments has progressed well and is exceedingly interesting. Dark-field visible agglutination of filaments by antisera is most impressive. Thick filaments composed of "bundles" of filaments appear on certain seeds. By limiting dilution passage in de-embryonated--or embryonated--egg the filament character remains stable. High-concentration passage, however, leads to selection of more viable but less filamentous variants...a wonderfully clear lesson in elementary genetics and evolution theory.

Eric French has just isolated a neurotropic agent which complement fixes like Jap. B or MVE from glycerinated brain material sent here from Port Moresby, New Guinea from a native. He has not yet done the neuts on it. Shortly after arriving here I found an old account of sporadic cases of acute encephalitis (which left no doubt that they were viral encephalitis from the detailed clinical reports) occurring in southern New Guinea. Eric's isolate may (??) give us the information needed as to whether MVE or Jap. B -- or an intermediate -- is present in these islands.

There has been a large-scale epidemic of almost afebrile, very mild rash disease, occasionally associated with arthralgia and mild arthritis and acute in course with recovery without sequellae and usually a non-incapacitating course in the Murray Valley this month and last. Over 1000 cases have been seen. The rash is dramatic. S.G. Anderson and French have thus far failed to get an agent. It is obviously sporadic, non-contagious and related to the ecological region of the Murray Valley. Rash is sl. puritic, often spectacular, usually vesicular and papular (cross between varicella and rubeola). Eggs and animals have thus far been negative. Specific rickettsial aggluts have not yet been done.

Eric French has made his isolation on CA membranes (of the MVE-Jap. B?) as he usually does. Since the CAM is insensitive to neutralizing antibody he insists that Hammon and others have finally agreed with him that it is a better route for neurotrope isolation than is the mouse brain -- even that of the suckling mouse.

This then is the current "gossip" which should be of interest to virus workers in the U.S. Thank you again for all of your help.

/s/ Carleton

[WEHIMR]

June 7, 1956

Dear Joe,

I am preparing to leave for the Cape York Peninsula and thereafter for a brief medical field survey--to supplement an intense ethnological-anthropological study which has been made over the past two years--of the West Nakanai peoples on the northern coast of New Britain. This trip will bring me to New Guinea and New Britain after the work with the aboriginal populations of Queensland is completed. In all I shall be away only a month or so. I am financing the trip from my limited private funds, although the Polio Foundation may (??) eventually see fit to pay my air transportation costs to Queensland--I hope! The venules you gave me form the backbone for whatever serum collecting I may be able to get done. I plan to return to the Islands for more extensive work later this year...and this preliminary trip is but a survey venture in order to make more specific and sensible plans at the time I apply for some financial support for the venture. If the later field work is supported, the cost of the current one will have been well worth it.

I write at present to enclose a copy of the Kodachrome reproductions as they will appear shortly in *KLINISCHE WOCHENSCHRIFT*. The proofs along with the captions which I wrote for them (they will be, of course, in German in the article) are enclosed. Although all of our correspondence was about having the pituitary gland in the lower right, I see from the proofs that they have made an error and selected the adrenal gland. I never did see the slides you chose, but I certainly cannot make out a pituitary from the lower right picture. I am right, am I not, that it is the adrenal which has been selected by mistake? This is not a very important error, and I have told them that the plate is satisfactory. I have suggested, however, that they consider adding the more important pituitary pathology in an additional small plate. This may well be asking too much. Will you please check my captions and let me know if there are any mandatory changes? Most important, perhaps, is some explanation of the middle picture on the right (2791) which is that showing epicardial petechiae and ecchymoses. What is the fatty reflection below the heart? Is it reflected pericardium, omentum or what? The yellow fatty sheet filling the lower third of the picture makes little sense to me or others...it appears to have hemorrhages in it. If it is reflected pericardium turned down, it appears mighty large for that. If it is omentum or liver surface it should hardly have this appearance or location. Can you explain it or find someone who can?

The charts and maps...duplicate proofs...I am also enclosing in order that you may see the neat job the Germans have done on them. Finally, there is a sheet with the English version of a short addendum which has been added to the section summarizing other hemorrhagic fevers at the end of the article.

I wish to thank you again for all of your help with this paper. Please let me know what you have done with the Omsk and Crimean viruses. Have you had any further word from the Russians? I now follow Russian conversation much better than previously and read it a bit better, but my speech is still highly ungrammatical. I certainly hope that I may someday have a chance to visit their laboratories and pediatric centers. I think that I know just which ones to ask to see--something which many who visit Russia apparently do not know--and from reports I have of recent Australian visitors, the Russians are quite willing to take them wherever they have sense enough to ask to go.

As I told you, I am working on infectious hepatitis immunology full time at the bench, and I have some interesting leads which will certainly demand intense follow-up. I hope to discuss all this work with you shortly. I think it is very promising. It will be my full time endeavour for all my remaining work in Melbourne, and this trip north will interrupt it but briefly.

Let me know about the stack of papers I sent you earlier in the year. I know that they demanded a huge amount of additional work, but for several months I have had no further word about any of them: South American serum survey, Middle Eastern survey, or Uruma virus study and Polio antibody studies.

Your new job must leave little time in which to follow diverse wanderings such as my own. I am in the habit of letting you know what I am up to and of soliciting your advice which I value greatly. I trust that you will permit me to maintain the practice.

No agent has come from the rash disease epidemic in the Murray Valley. The MVE or Jap B strain Eric French now has from New Guinea (formalized brain material) has not yet been checked by cross neuts but will be shortly.

Sir MacFarlane is most interested now in the problem of immune tolerance, skin grafting, and the possible immunological mechanisms which govern normal cell proliferation. These latter may have much bearing upon the cancer problem. He is into skin grafting work and other such matters. This entire field has much promise and I am already working out a set of crucial experiments I should like to try on premature infants and newborns--totally harmless yet totally definitive--about which I shall write to you shortly.

Sincerely,

/s/ Carleton

D. Carleton Gajdusek, M.D.

[WEHIMR]

28 September 1956

Dear Joe,

I have recently returned from New Britain, the Trobriand Islands, Samarai, New Guinea and Papua and Fergusson Island in the D'Entrecasteaux Archipelago. Your letter awaited me and I am sorry that I am answering it so late....for it contained much that I should have replied to sooner. My three and one-half months of field work was immensely profitable. I managed to collect blood specimens from 600 aboriginal children of the Cape York Peninsula and to confirm the measles story about which I have told you. Thus, these sera await careful study for measles CF and neut antibodies by tissue culture techniques and promise to yield information and an evaluation of the measles seroepidemiological tool which no other collection I know of could yield. Obviously they are ideal for studies of duration of antibody after acute infection in the absence of reinfection, since measles disappeared from the population completely after each epidemic. The specimens can also be used for all other seroepidemiology (dengue, Jap B, MVE, etc. come to mind immediately). I am using them also for gamma globulin, total protein, serum electrolyte, etc. studies to correlate these data with the child growth and development, chronic malarial and hookworm, and nutritional survey I made among the aborigines. An intensive blood group genetic study of them has already been completed on the red cells (MN, P-factor, Kell, Duffy, Lewis, Diego--a new factor--, et al including the usual ABO-A₁, and Rh subgroups). Best of all, I was able to get a long-term longitudinal child growth and development study started with a good selection of aboriginal children and infants as subjects who we should be able to relocate in future years.

Most of my time was spent in the islands, however, rather than among the aborigines. I concentrated on four tribes in the Territories: the Orikaiva eastern Papuan jungles (of Kokoda trail notoriety for having shown the Japs the hidden trail across the "uncrossable" Owen Stanley range after having delivered to them their missionaries for beheading on the beaches), the West Nakanai and the Central Nakanai of the northern coast of New Britain (the West Nakanai the subject of the joint Australian National University-University of Pennsylvania intensive ethnological-anthropological survey of a Melanesian culture and thus with a currently studied anthropological and sociological background for any child growth studies I set up among them); and the Mamusi of the central jungle-covered mountainous interior of New Britain. With the West Nakanai and the Mamusi I lived long enough to learn much of their languages and become very familiar with their way of life. The Kakuna Mamusi I reached after a long expedition, and finally established myself as the first white man to visit some of their villages...only one Caucasian had preceded me into the Kakuna region of Pita, and Waralo, the Catholic missionary and I concentrated most of my work on them. They lengthen the skulls of all their infants by a tight restrictive binding technique before the sutures close. Thus, I was able

to make a fine study of the effect of this cranial vault deformation on the growth and neuromuscular development of their infants (it appears to be nil). Besides setting up child studies aimed at long-term, longitudinal follow-up in each of the four cultures, I brought back a few hundred serum samples. The red cells have already been used for a genetic blood group and type survey like that done on the aboriginal specimens. The hemoglobin from the clots is still on hand in case I can find anyone interested in doing abnormal hemoglobin determinations (paper electrophoresis), since this Melanesian populace would be most interesting in view of the high rate of Hemoglobin E in Siam and Indonesia. All sera are stored here at -25°C.

Although I have managed to do some herpes and mumps screening on the child blood specimens, I am doing nothing else with them for the moment. Anderson and French are rushing through the MVE problem; but not other neurotropes, since they have a strain of MVE (it was not Jap B) isolated from the brain of a sick native at Port Moresby which was sent to us here in glycerol. Serological screening of their serum collection locates MVE antibody in some population groups, but not all, scattered in Papua.

My own work is back on infectious hepatitis. I have some interesting leads and developments about which I shall tell you in a future letter. Even news of IH cultivation in Detroit 6 cells does not discourage me, for I now am on quite a different aspect of the problem from that of the cultivation of the virus. I can not possibly finish this work by November, and thus I have extended my stay with Sir Mac for 3 months...and I shall return to the U.S. at the end of the year.

I have written to Nancy requesting that she send me the manuscripts on the South American and Middle Eastern serology papers. The South American paper was really in final form when I sent it back some 5 months ago---you had already revised it---and the Middle Eastern paper required only pruning, which I can easily do. Should you see her, please urge her to send me the drafts, for I can and will work on them and whip them into shape. I still have requests for data which we have from Turkey, Iran, Peru and Bolivia about the work, and I believe that the findings are of enough interest and importance from the local tropical public health point of view to be worthy of more extensive documentation than the note in the Federation Proceedings which dealt with polio only---the least interesting part of the serology.

I am enclosing a reprint of the German paper on epidemic hemorrhagic fever which is, I believe, adequately up to date in that it covers all publications of which I am aware and includes the new Russian claims of Omsk virus-RSSE serorelationships. I thank you for all the help you gave me with this, including the selection of the fine Kodachromes. I trust that the AMSGS ordered copies if it wanted them. I mentioned this matter to you several times in the Spring. We have several hundred on hand here, but it appears that most will go in reprint requests.

French tells me that MacCallum passed through Melbourne during my absence and told him of new U.S. work incriminating Welchii toxin in EHF pathology. It sounded very fishy...but, I know full well the possibility of a toxin rather than an active proliferating microorganism at the site of the lesions has seemed very possible. What is the story about this? Also, can you tell me what you have found with the Omsk and Crimean viruses from Russia? Is Omsk identical with RSSE or a variant? Is Crimean related to RSSE?

What has happened to our Uruma virus report? A year ago it was worked up fairly well as an independent agent fairly definitively associated with human disease...we even have a fair idea of the disease! The link of it with the Rockefeller viruses and the slight relationship to Semliki Forest were established! Is the report coming out...has it come out?...and can I get to see the revision of the draft I sent in? In all probability these are questions I will have to address to Schmidt and Edsall...and I shall write to them shortly. In the event that you know anything about the matter when you next write, however, Joe, I should appreciate the news.

Finally to the most pressing part of my belated report---at least to me personally. I have not yet decided upon work when I return to the U.S. I shall be returning in the early Spring 1957. It is probable that I should try to get the measles antibody work done on the aboriginal sera I shall send back, and this might best be done in Boston. Whether I shall get involved in other serology on the aboriginal and Pacific Island sera or not I have not decided...and am quite prepared to turn this over, in part at least, to those whose specific interests apply to them. The immunological problems which I have become involved with in the study of infectious hepatitis, chronic hepatitis, lupus erythematosus and the collagenous diseases are interesting, extremely important to microbiology, and obviously one of the most pressing problems of modern medicine (there is no point kidding ourselves which is more important...the acute virus disease or the prolonged immunological disturbances of rheumatoid-lupus-chronic hepatitis-collagenous diseases, etc....and the study of the immune response now necessarily impinges closely upon all serology and immunology...including viral, as is amply evident in both hepatitis and the Group B encephalitides). Where I shall leave my current problem I do not know. I probably would like a chance to go on with it in the U.S. or elsewhere, for a while.

By way of a hobby, I have now set up child growth and development studies which can easily become meaningful longitudinal studies if the same children are again seen in follow-up, in several continents. I would like to keep up this hobby and, if a really good opportunity to carry through this comparative cultural child development program did show up I would be anxious to accept it. Therefore, Joe, I am still interested in "chasing the Indians in the Amazon Basin" and South American populations interest me particularly. I speak the language, get along well, and know my way around fairly well in Latin America.

If the NIH is really interested in further tropical virus disease study...and if I can get some leeway in pursuing what I believe are equally important interests...comparative child development in different races and environments... I would be very interested in a position with NIH which would give me this chance. As far as wanting to roam continually, year-in-year-out--NO! I am not physically up to it. In the past year the three months of jungle expedition across New Britain and living in the native villages were enough. All I ask is not to be restricted to week-end beach parties year-in-year-out. I believe I have made every expedition I have made pay scientifically. I would like to continue to do so. That demands a base of operations and time to sit and work and think and organize field work! A base laboratory or institution is essential!

Thus, Joe, I frankly am shopping and trying to find a place to continue work. I do not want to remove myself from pediatrics at any cost. Tropical infectious disease, even the immunological research I mentioned, and most virus work keep me involved enough clinically in pediatrics to satisfy me. If you have any opportunities wherein I can fit...and you know well what a recalcitrant and unpredictable subordinate I make...in which I can let my interests and imagination have some play, I shall be most interested and grateful.

Thank you again for your continued interest in me and my work. I am grateful and thankful for your friendship. Please send my greetings to your wife and to any of those whom I know in Washington. When you next see Woodward and Wisseman tell them that I shall try to write eventually.

Sincerely,

/s/ Carleton

D. Carleton Gajdusek, M.D.

[NIH]

December 11, 1956

Dr. D. Carleton Gajdusek
The Walter and Eliza Hall Institute
of Medical Research
c/o Royal Melbourne Hospital Post Office
Melbourne
Victoria, Australia

Dear Carleton:

Sorry to have delayed so long in answering your interesting letter describing your trip to the wilds of New Guinea, et al. It must have been a rough but worthwhile venture. I shall look forward to hearing about it at first hand and in detail with kodachromes.

I am sure you are taking good care of your valuable serum collection. Are you planning to persuade Enders to do the measles antibody tests or to do them yourself in Enders' lab? The residual sera should probably go to Charlie Wisseman for file and eventual testing for various members of the B group after Anderson and French have finished the MVE titrations.

I have no news on your three or four papers which were still in various stages of development when I left the School last April. Casual inquiry on several occasions elicited no definitive information. I suggest all or most will still be waiting for final touches and a final push when you return to the U.S.A. Incidentally, I note that you expect to be back by the end of the year but knowing something about your habits, I suspect that urgent business will detain you in Australia. I shall really begin to look for you in the spring.

The German review with the colored illustrations looks fine. Don't buy the rumors about Welchii toxin being involved in the pathogenesis of HF -- poor work -- no control. The Omsk HF virus was received and studied by Schmidt who found, as Chumakov said, it to be indistinguishable in the laboratory from RSSE. The Crimean virus specimen did not prove viable when tested in one of Woodward's volunteer patients, so it was not surprising that monks and some half dozen types of tissue cultures also drew blanks.

We are progressing well with plans for a Tri-Service Laboratory (NIH-Army-Navy) in the Canal Zone under the cloak of the Gorgas Memorial Laboratory. This should develop into a good field organization for study of arthropod-borne virus infections and other diseases of medical importance in Latin America. Willard Wright's Laboratory of Tropical Medicine of the NIH will be the focal point for our efforts in the field and will develop a section to serve as base laboratory for the field (along the pattern of the School serving as the base

for the Malayan Unit). I think you would fit well into this general work and into the new group Willard is developing. I talked to Willard about you and he is definitely interested in discussing the possibilities with you. So, stop in when you get back. I think there is a place for you in the NIH organization and that you would be an asset to the NIH.

Very best wishes and Seasons Greetings.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director
National Institutes of Health

cc: Dr. Willard Wright

The Walter and Eliza Hall Institute
of Medical Research
c/o Royal Melbourne Hospital Post Office
Melbourne, Victoria, Australia
December 29, 1956

Dear Joe,

Enclosed is a small pamphlet, available in the Russian language distributing houses here for about three American cents, which is entitled "Spring-Summer Tick Encephalitis" by N.N. Gorchakovskaia. It is published in 1956 in Moscow and includes the tick- goat-goat milk cycle as well as the rabbit- tick- tick-bite- man cycle (see picture, page 19). There is so much of this sort of stuff, and stuff of far higher academic caliber now rolling off Soviet presses, that I am utterly astounded.

Thank you for your recent letter. I was anxiously awaiting word from you before making any plans. Now I shall delay permanent plans until I have a good chance to discuss matters with you in much detail. I hope to terminate my work here in early February and to return to New Guinea, New Britain, and other islands for further pilot studies on child growth and development in primitive cultures. I shall also collect further serum specimens, no doubt.

Dr. Enders has voiced his willingness to let me continue my work there in Boston and I shall investigate the measles antibody problem in Boston, as well as other serological work on the Melanesian and aboriginal sera. Already I have done herpes and mumps and, in addition, some biochemical studies which indicate a very great departure of all of the Melanesian sera from normal levels of gamma globulin and, to a lesser degree, of the aboriginal sera as well. This is not so in the bloods of small infants. My sera are ideal for study of this matter and I believe that it will eventually be correlated to the extent of exposure to pathogens of all sorts, including malaria, by everyone growing up in these cultures. It certainly has bearing on serological epidemiology both theoretically and practically, since these high gamma globulin sera behave differently in complement fixation to normal control sera with low gamma globulins. More about this later. I cannot publish any of this material until I get it all organized back in the U.S. and it is about that that I will talk to you once I return.

The blood group genetics data is completed and will be in press before I leave Australia. So will, I hope, a few pediatric notes about skull deformations in infancy with displacement of the developing brain, and similar esoteric oddities gleaned from the islands. The more meaty studies will have to await further work.

My last three months have NOT been spent on these matters, however, but rather on a new phenomenon which I turned up by accident while working in my quest for infectious hepatitis antigen. It was a fluke in my reactions, and by investigating this fluke I have invaded the entire field of auto-immunity, iso-immunity, tissue and organ specificity, self-marker hypotheses in both cancer work and embryonic development, and the matter of immune tolerance as it enters into skin grafting, theoretical immunology, and the body's recognition of its own cells (i.e. cancer "escape", etc.). Sir Mac and everyone hereabout is most excited by this new find, and I have rushed ahead with it day and night since I turned it up. Already a note is off the Nature covering the original findings. A much more detailed account will soon be in press. However, Joe, it is the first really original and important thing I have turned up and I do want to get it out and followed-up before everyone else swoops down upon it. I am enclosing a manuscript of the work for your comment and suggestion, but beg you to treat it confidentially until I get a bit further along with it. I shall also send you the definitive manuscript which covers much more extensive work in acute infectious disease, infectious hepatitis, auto-antibody presence in supposed "normals", and a host of similar phenomena. The excitement about the work in our clinics here appears to be justified in that it offers many a new approach... even to studying the development of organ specificity in embryology. I am already on these trails. Obviously, Joe, this is not something I can afford to drop, and upon my return, although many another interest will take my time, this problem is the one on which I stake full claim and for which I shall need time and facilities. It may fizzle out in time, but for the moment, it looks good, and by an intense study of a few highly intriguing sera, I am already breaking into the antigen composition of normal tissues and organs. The entire problem of false positive Wassermans, of Heterophile antibody and Forsmann antigens, and false positive (so-called "non-specific") CF reactions are all tied up with this matter.

I shall be very interested in any comment you can make on this note which is off to Nature. Furthermore, I shall be most interested in your advice as to what American journal I should aim at with the definitive article, now ready for publication. Journal of the AMA? Medicine? Journal of Exp. Med.? Journal of Clinical Investigation? I am sole author of the work...although a dozen people here, including Sir Mac, are standing ready to pounce on the problem with my departure, and my clinical associates will have a note on clinical correlates which may be ready to follow my definitive paper. Thus, Joe, if you can blow a hole into my early and probably premature enthusiasm, please do so now. If you think there are all the possibilities in this approach which I believe there are, let me know. Keep the Nature paper and gossip about this confidential--for only you and Dr. Enders know of it in the States (and perhaps Jordan, who was with us and is now back in Cleveland).

Another favor: I shall be ready to send the rather large file of sera from the aborigines and from the Melanesians to the U.S. shortly. If I could address them to you and have them stored in NIH freezer-space, I should be most satisfied with this arrangement. It would probably simplify Customs matters, pickup, and storage, considerably. Would you be willing, and, if so, exactly how should I address them? If you think they should go rather to Walter Reed, let me know. Those that I shall now send are collected with my own venules and separated and frozen (they are now at -20°). I shall use the venules which Dr. Edsall posted to me sometime during my return to the islands in February.

In March or April I shall stop by at Kuala Lumpur. Please let them know thereof, should you hear from Pond, Traub or others. I shall write to them also. I plan to return to India, Afghanistan, Iran and Europe, and arrive in the U.S. before the summer or in mid-summer, ready for full-time work.

Although the serological investigations, as well as my autoimmunity project are obviously going to keep me tied up with fundamental laboratory research for some time, I am most anxious to keep free for a more permanent assignment, and I look to South America with every bit as much enthusiasm and interest as I had before I last left the U.S. Please, Joe, keep me in mind, and especially if the project can embrace my ethnological, pediatric, and medical research interests simultaneously. Although I want enough authority to go my own way as much as possible, I should still like to shun administrative responsibility of the type which "ties one up". You know what I mean.

Again, Joe, I thank you for your continued interest in me and your kind attention to my many requests. I hope that all goes well for you at the NIH and that you and Mrs. Smadel are in good health. Send my greetings to Danauskis, Betsy, and the others.

Sincerely,

/s/

Carleton

P.S. My passport...as all U.S. passports...is now clear for the USSR. My knowledge of the language, literature, and places is better than ever. If you can think up any good reason for visiting the USSR en route home (I shall both be under its soft under-belly in Central Asia and on its European borders during the spring) please let me know. I think I would find little difficulty getting around, seeing plenty, learning much, and exchanging ideas. Not being myself aware of anything "classified" I ought to be a "safe" exchange ambassador with enough time to spare to learn what wisdom our Soviet colleagues will pour out.

Nancy says that Beuscher has the manuscripts tied up "in the office" and no doubt I shall have to await my return to the U.S. to straighten them out. However, if you see him, urge him to send me the near-complete ones post haste, for I might well polish them off before leaving here.

/s/ Carleton

Moke...at the Okapa Patrol Post.
Forei, Kimi, Kei'agana Linguistic Areas,
Territory of Papua and New Guinea

15 March 1957

Dear Joe,

Enclosed is a somewhat self-explanatory letter. I am in one of the most remote, recently opened regions of New Guinea (in the Eastern Highlands), in the center of tribal groups of cannibals, only contacted in the last ten years and controlled for five years--still spearing each other as of a few days ago, and cooking and feeding the children the body of a kuru case, the disease I am studying--only a few weeks ago. This is a sorcery-induced disease, according to the local populace, and that it has been the major disease problem of the region, as well as a social problem for the past five years, is certain. It is so astonishing an illness that clinical description can only be read with skepticism, and I was highly skeptical until two days ago, when I arrived and began to see the cases on every side. Classical advancing "Parkinsonism" involving every age, overwhelming in females although many boys and a few men also have had it, is a mighty strange syndrome. To see whole groups of well nourished healthy young adults dancing about, with athetoid tremors which look far more hysterical than organic, is a real sight. And to see them, however, regularly progress to neurological degeneration in three to six months, usually three, and to death is another matter and cannot be shrugged off. If psychological, we have the very best epidemic psychosis for study in the world, and the Institute of Mental Health should be most interested. If a heredo-familial disease, we have the highest incidence concentrated "epidemic" ever seen, and the human geneticists should be "on the ball". If a post-encephalitic or toxic or allergic encephalitic epidemic of basal gangliar disease is here, then all of medicine should be interested.

The P.H.D. in New Guinea is interested, and Anderson and the others at the Hall Institute have been corresponding with Dr. Zigas here, who found the disorder over the past two years and has seen it consume to a fatal outcome the child and adult alike...it is no chronic senile neurological degeneration!

I am now on the spot in being in the Territories and in the process of setting up further child growth studies in primitive cultures. Obviously, I have the study on my hands at the moment and, in any event, will be a collaborator in whatever goes on in the future. However, Joe, I stopped all my polio fund salary when I left Melbourne in February, and since January will have no income until I finally get back to the States. I am now living off my small savings and have no grant at the moment, with plenty to do in a dozen fields on my return; however, this is nothing to put off and nothing to drop. I write to let you know about it firstly, and secondly, to request whether there might be a grant you could dig up. I am in no position to make a more formal application, being devoid of mail, radio or telephone and all else in the bush, where I am working on the disease--but with astoundingly good native hospital, clean mountain top, jungle surrounded native buildings to keep the sick, and sometimes even serviceable jeep track to import supplies and rations from the government. All I need, however, is enough to insure my keeping alive once I get out, if this runs to several months, as it certainly should, if I can afford to stay. With no initial expenses of equipping an expedition, or

shipping off supplies or personnel, might there not be some Public Health Service grant, or any other you could find to give me some sort of salary while I work here? I could already give you a set of papers on a truly new disease. If all this is impossible, O.K.

May I send to you specimens and blood serum, etc., if it proves feasible? Most are now going to Melbourne. I would not pre-suppose this to be an infectious disease problem. Briefly, some fifty people have died of the disease in a small community within two to three years (children included), all with the same neurological picture, afebrile and progressive, and some four doctors beside myself have now seen it. We are all impressed that it is a new epidemic syndrome of some sort of Parkinsonism, or basal gangliar disorder (toxic, allergic, heredofamilial, post-infectious, infectious?--or psychiatric)? If the latter (psychiatric), its study would be most important.

Although the people are still current warriors and cannibals, they are well 'under control' and very cooperative; language is no problem for good Pidgin English translators are available for each language and I am already at work studying the languages. My auto-immune complement fixation test paper in Nature should be out any day now. The definitive paper was submitted to JAMA before I left, and a second paper with clinical correlations will now go in. A third on the auto-antibody nature of some macroglobulins and on the characterization of organ specificity, of antibodies and antigens in certain diseased sera of high titer, will soon be ready. It is work that I must go on with, but since I left, Sir Mac has converted most of the institute work to this type of auto-immune study, and my AICF test will soon be followed by a barrage of Hall Institute publications, I believe and, to be frank, I fear. I have a paper in manuscript form on skull distortion in infancy, and its effects on development, as studied last year among the Mamusi and Arawe 'savages' in New Britain--and sundry esoteria. The current disease study on kuru is no esoterium, however.

Should you be able to think up even a nominal salary or grant for me for as long as these studies are underway, or to reimburse my maintenance expenditures while I am undertaking this, please let me know. My address is: c/o the Director of Health, Department of Public Health, Port Moresby, Territory of Papua and New Guinea. My current location for a cablegram is the same, or more directly to: Okapa Patrol Post, Kainantu S.D., C/O A.D.O., E.H.D., Territory of New Guinea.

Joe, I had planned to write about much and at leisure during my New Guinea field work, but this has me now rushed beyond all hopes. Since I would like to be able to stick to it, I must request your consideration for any possible, even moderate financial support while it goes on. The last two months have been without pay; I am by no means broke as yet and with or without help, I intend to stick this one out a bit. Greetings to everyone at the NIH who may remember me, and to the WRAMC crowd. I hope I will be seeing you all later this year. The *Pneumocystis carinii* paper should now be out in Pediatrics, much as you saw it last year. The parasite has now been found in Melbourne and in Sydney in infants' lungs...how about the U.S.A.? If and when this is finished, I have a brief field survey of possible child studies in Dutch New Guinea on tap. Shall I send sera to K.L.?

Sincerely and gratefully yours,

/s/ Carleton

Moke (incorrectly called Okapa)
15 March 1957 (in the pouring rain)

Dear Doctors Burnet, Anderson and Wood,

I realize that my last letter, written rather spastically in a great rush, calls for prompt follow-up. Since we are trying to get a Jeep out (Dr. Zigas will go and I will stay) tomorrow, I am writing now, although landslides may have now blocked the road and made exit impossible for a few days.

At Kainantu there were two old women from Moke (called Okapa by mistake although Okapa is really another settlement) who had kuru. They had been brought to Kainantu for Dr. Scragg to see when he visited Kainantu (he did not come to Okapa) and had classical advanced disease. When I saw them they were no longer ambulatory and the tremors, athetoid movements, blurred speech, all pointed to a chronic neurological disorder unassociated with any acute infectious disease at onset, or even in the months or years before onset, which was dramatic enough to be recalled by reliable informants in their community. They were rational, but articulation of speech was very poor. Silly smiles, with grimacing, were prominent. Fixed and pained facies and slow, clumsy, voluntary motion, apparently in an attempt to overcome tremors and athetoid movement, were prominent also. They were carried to our Jeep and managed to hang on, sitting up for the four hour rough drive here. No fever during the course has been noted and the story of headache and "skin it" is very variable and uncertain at onset. I was certainly not able to say anything but ? Parkinsonism...a rather apparent disturbance of the midbrain and basal ganglia in the older women, with no real cause for believing it post-encephalitic.

Now that I am here, the picture is shaping up better in my mind. We have been collecting all the cases we can in the entire region. I am getting detailed anamneses, which requires a half day of work on interviewing each case, and it is already apparent that the majority of cases do not have acute onset and no acute febrile disease suggesting encephalitis in any way has been present in the region, as seen by patrol officers or by Dr. Zigas, or recognized by the natives or early patients. As Dr. Zigas had noted, the picture is astoundingly uniform and distinct. Native diagnosis of kuru is as reliable as any modern medical appraisal would be. They know what they are talking about, and once you have seen a few cases you also know. However, nothing in the course suggests microbiological studies, I fear. Instead, Sydenham's chorea comes to mind first; secondly, various types of hysteria and motor aspects of psychoses, such as behavior of certain schizophrenics, but the hysterical analogy is closer for rationality is usually good early in the disease, as well as late. However, as it progresses, neurological damage appears to be rather certain, but it is most difficult to pin down, now that I have been doing very complete neurological examinations. In fact, cerebellar function tests are very mildly disturbed, if at all, and the whole picture would be mesencephalic or a basal gangliar disease. The predominance in women is most marked, a ratio of between five to ten to one, perhaps higher. This is so certain that coupled with the picture, one must think of heredofamilial neurological degeneration of which texts are filled, with dozens of eponymically designated syndromes. The incidence is spread over two linguistic groups--clans which often intermarry. A third linguistic group also bordering on this region of tri-linguistic junction may have had a few cases in villages directly

adjacent to the kuru region, which appears to be rather small, but further study is required. The fact that Parkinsonism has been seen in natives in Goroka was revealed to me at Goroka by Dr. Symes, but the story of kuru at lufa is new to Dr. Zigas and he questions it, since he was there himself.

On arrival here, I concentrated on two classical cases in middle aged women with all the features which have been described to you. This morning I did thorough physicals and neurologicals and found no truly abnormal reflex patterns, sometimes slightly hyperactive, other times slightly hypoactive triceps, biceps, radial periosteal, tibial, no abnormal reflexes. One of the severe cases seen yesterday, unable to walk and with extreme tremors and athetosis, has been walking about most of the day, without a sign of disease, and it is thus certain that rather advanced symptoms can reverse overnight at this stage. One naturally keeps thinking of hysteria or anorexia nervosa type disorders (in this there is no anorexia) but the eventual outcome to real debilitation, tremor and athetosis and speech disturbances beyond reversability is likewise certain. Thus, I prefer to believe that the reversal I have so clearly seen in one typical case overnight is part of the exacerbation and remission of a basal gangliar type disturbance, with different levels of emotional excitation...the "remitted" patient still had tremors at one time during the afternoon.

Naturally, all this makes me fix my attention on my own domain, pediatrics, in which I consider myself rather competent as a neurologist. There are childhood cases which end fatally, I am told, and I have tried to see them. One child, a boy of about seven, had been carried here; he is, obviously, unlikely to survive for long, can no longer walk, has hardly distinguishable speech, and urinates and defecates in the house, although he is not dribbling nor incontinent. As with all cases, he has to be fed now, having lost the ability to bring food to his mouth. It is hard to believe that he is a recent case--a boy previously of normal intelligence and physical development--but multiple reliable informants testify that he was walking, running and playing normally only three months ago. His speech and growth and his development were apparently normal. The course is that described for classical kuru, i.e. one month of unsteady gait followed by tremors and athetosis and blurred speech in the second month and, now, in the third month almost complete incapacitation. He is a nice cooperative fellow, a bit too far gone, I fear, to consider taking to Melbourne, unless a doctor accompanies him.

Today, a ten year old girl, intelligent and cooperative, was brought in in her second month state, marked tremors, instability which was marked with slight athetoid movements...I examined her completely. She had no adipokinesis, only slight disturbance of finger to nose, finger to finger, or heel shin cerebellar function tests and negative Rhomberg. Her speech sounds O.K. but natives assure me that it is blurred, yet fully rational. Optic fundi are normal, as are those of all seven typical cases I examined thoroughly today, and there is no papilledema, retinal exudate, cupping or blurring of disc and no optic atrophy; no nystagmus or extraocular motion abnormality in this girl, nor in the other six; pupillary reflexes to light or accommodation are normal. Lumbar puncture on the girl with immediate and repeated cell counts: RBC 40-50/mm³ (fresh from slight trauma of tap); WBC₃₃ 6/mm³ (fluid clear and colorless); WBC checked by acid solution of rbcs 5/mm³; Pandy negative; heating (boil) and then Pandy reagent, slight trace of protein. Thus, normal WBC in peripheral blood about 6000/mm; slight but not marked anemia. I shall try to get urine etc. tomorrow. Before fluid was removed dynamics were checked and found to be normal, and pressure was also normal.

This case is now in the second month, a most typical case, and as with most others there is no sign of encephalitis onset, although by questioning for hours, we have elicited the story of an acute stomatitis in the boy of seven just before his onset (? herpes simplex), and in the girl now in question (some headache and "hot skin", which never really kept her from play) at onset (? did we put it there by the intensity of interrogation). That no one has seen an acute febrile disease they associate with the onset of kuru, and that we have found none, is now certain; there has not been an epidemic of any sort, although rubella was said to have gone through the region no evidence that these cases were preceded by rubella, however, was pointed out, although it could be. Thus, it seems further apparent that microbiological field epidemiology, although perhaps indicated, is not the primary nor most important line of attack at the moment. Good clinical and laboratory pathology is the current need in deciding what this is. Thus, I still urge high grade hospital workup with thorough neurological consultation and long term followup (a total course is three to six months to death in most cases, although I have now located "cured" cases of the once-classical kuru). I can do as much field neurology as any neurologist, I feel, but further accurate chemical, encephalographic and x-ray studies, and serial neurological observation with good neuropathology on autopsy material are the primary needs.

We shall do our best to secure whole brain, fixed in 10% formol saline, on the next death. There is little to suggest pathology in any other system, but we shall try to get other fixed viscera also. Virus isolation material will also be sent, but it would appear highly dubious that anything microbiological would be found in these afebrile, chronic, progressive neurological degenerative conditions. Neuropathology, using every available technique, is essential...since most cases die, and those now on our hands probably will also, please send detailed and exact formulae and handling methods for brains, as determined by an expert neuropathologist. Many prefer long term fixation before cutting of brains, fixation being on the whole brain. For silver impregnation special fixation may be required. Please be specific, since reference works to check the formulae are not here. Should we find anything that even remotely suggests a possible kuru antecedent infectious disease, I shall rush to you all possible tissue and washings for isolation studies, but no signs thereof as yet, nor in the past. A year or two of residence might be required to settle the matter.

We have already located familial cases occurring years apart, with a mother and sibling (older sister) of the ten year old girl I have written about, having died of classical disease five and three years ago, respectively. Please consider carefully the possibility of accepting in Melbourne this ten to twelve year old girl (her age could easily be stretched to thirteen or fifteen years for the purposes of Royal Melbourne). We think ? we could persuade the parent (father) and the village to let her go, and we could send with her a very intelligent sixteen to eighteen year old lad who is native Forei in speech, fluent in Pidgin, and a good translator, and one who wears clothes well. The girl herself is ambulatory, cooperative and a good patient who could still travel easily. All evidence points to a progression beyond this favorable point within one to two months, if she remains here. Thus, faced with a fatal disease and with a young cooperative patient on hand, with about as early a case as one can have with kuru, this is the case for you, if ever you want one. Please send us word directly, and if it is yes, start immediate arrangements with Drs. Gunther and Scragg, telling them of our progress, since you are better informed now than they. I shall write a brief report to

the Public Health Department in Moresby now. Our work in plotting out the lineage and location of cases, the study of cases on hand and the hunt for new cases and the therapeutic attempts on those on hand--long term doses of vitamin B complex, ascorbic acid and chloramphenicol--truly a shot in the dark! If we can get it, we may try ACTH and cortisone. We have not recorded a single even slightly elevated temperature; no sedimentation rates have been done as yet.

Excuse this disjointed report...Dr. Zigas and I are rushed, and he states that he can only remain a few more months in the region before taking leave, i.e. at Kainantu. No kuru at Kainantu, but we shall certainly bring cases out and head for Moresby, if possible; best of all would be Melbourne, for where in Moresby are we going to get reliable pneumoencephalograms and, especially, electroencephalography, which can be of value in suggesting post-encephalitic damage, reliable metabolic studies, or endocrine studies? What you need is good neurology, laboratory pathology, clinical pathology and neuropsychiatry. It would be cheaper in the long run to send you a good case, and in a child, it would be manageable...we are trying now to get dresses on her. The P.H.D. and Dr. Zigas would like to know of your plans. We can undertake anything you desire, at the moment, and should any of you want to see the disease in situ, come up promptly.

Sincerely,

/s/ Carleton Gajdusek

/s/ Vin Zigas

[Moke (Okapa Patrol Post)
Eastern Highlands, New Guinea]
20 March 1957

Dear Joe,

Here is a carbon copy of a letter to the Melbourne crowd which will add further details to my previous note on kuru. Do not worry if my request for some form of grant proves embarrassing, for I can struggle on my savings well enough until I get back to the U.S. and find a job. This is, however, obviously a good chance to see a rather rare syndrome en masse and should not be missed. Thus far Dr. Zigas, a Lithuanian emigré physician 7 years in the Territory and two years in the Highlands, who spotted the disease medically, and I are the only ones seeing and studying it.

Obviously, the Hall Institute has a stake in it, Anderson is particularly interested, but we need more than field virology.

Sincerely,

/s/ Carleton

Carleton

Moke, Territory of Papua and New Guinea

20 March 1957

Dear Drs. Burnet, Wood and Anderson,

While we are awaiting word or suggestions from you I thought it wise to avail myself of the opportunity to get mail out to Kainantu. We have now located some twenty-seven cases of kuru, all new, which were not present in October 1956 when Dr. Zigas tried to round them all up and found thirty-six (and bled twenty-two) in his three weeks in the region. All, or all but a few, of his thirty-six cases are now dead, but this check on deaths has not been fully completed as yet. Our twenty-seven represented a distinct pediatric concentration and, thus, we have rounded up eight cases in children who are now in the hospital. In addition, nine adults are in our special kuru hospital, and we plan to keep the children at least throughout the course of their illness or to recovery or death. It will be the latter, I fear, for some who are far gone already.

I have developed an extensive anamnesis technique and finding the natives as accurate and as good informants and observers as any parents I ever encountered in civilized pediatric practice, if one takes into account the two to three hour discussion a history requires. By this technique, it is now evident that kuru has been recognized here for at least two decades, perhaps longer. It has a traditional focus in a few 'villages', and has spread to a few adjacent ones in the last decade or so apparently, but this is not certain. There is no detectable seasonal incidence of onset, with cases appearing all through the year, but it will require more statistics before a curve to detect peak incidence can be plotted. I noted earlier the frequent accurate stories of kuru in the mothers of some of our patients. In checking this carefully, we found that independent observers agreed on this in their past history. By taking extended family histories it is now evident that there are multiple cases of kuru within the families of many of our patients, and the histories are filled with such other descriptive causes of death as: spear wounds, arrow wounds, old age "lapun tru", skin ulcerations, capture and stab deaths, abdominal disease, and diarrhea with bloody stools. Since these descriptions are given consistently and accurately, and since recall of kuru seems to be fairly stable in the minds of the villagers to the extent of acting out tremors and late incapacity, we must accept these histories as accurate. They point to our classical patients and say "the very same thing" in describing past cases.

Of the two children admitted yesterday, one girl of seven years had both of her father's two siblings die of kuru, and the patient's mother also died of kuru. The other, a girl of ten years, had had kuru in seven close relatives. Thus, although neither parent died of the disease, both of the two older siblings died of the disease in the past at the age of about ten years. Furthermore, one paternal uncle and three first cousins on the father's side also died of kuru, and one child of one of the paternal cousins also died of the illness. On the mother's side, we could find no cases of kuru. Now, whether this high family incidence is spurious because of a high incidence of the disease in the entire community, I do not know, due to the time-consuming nature of necessary 'control' histories. But, that there is a rather astonishing family

incidence is now clear. I am using Western relationship terms, disregarding native kinships. This can be done, since they understand well that we want the lists of "pikaninis blong wonpella bel", i.e, the lists of all pregnancies and children born to each woman or man involved--and they keep this straight in their minds! In spite of the familial incidence, with an almost uniformly progressive course which likewise suggests one of the heredofamilial neurological diseases, as does the greater than 10:1 predominance in females, we are finding stories of fever, malaise, headache, and knee pains, without the stiff neck and loss of ambulation (this is definite) in several patients, which might suggest an antecedent acute infectious disease. This is not, by any means, the case in all patients. Many had gradual onset without antecedent illness; none had incapacitating disease with sleep, coma, paralysis, meningeal neck stiffness, or any other symptoms which might have kept them off their feet. Thus, we have no suggestion of true encephalitis preceding the illness, such as the encephalitis lethargica which occurred after World War I in Vienna. In fact, rash illness, stomatitis (the one history thereof is unique), severe acute febrile disease, or any other such antecedent illness, is most certainly lacking. Thus, although we are disturbed and still trying to hunt down the febrile diseases which might be prodromata to this syndrome, we have not as yet found any ourselves, but will eventually make a house to house search during patrol in the villages.

Our hands are full in trying to keep charts and progress notes, records of medication (our clinical trials, in which I have little faith, but which we follow with true clinical investigative procedure), with feedings in the two advanced cases beyond self feeding possibilities. We have now completed lumbar punctures on fourteen cases, including all eight children. In no case did we get more than a very slight cloudiness with four drops of Pandy reagent, heated, in warmed cerebrospinal fluid. All pressures were in normal range, with normal dynamics (using 120-150 as normal). All fluids were clear and colorless; no pellicles formed. Careful cell counts on all fluids have been done, repeating the count completely three times on each fluid. None had over 10 WBC/mm³ in early or advanced cases! Red cells from slight tap traumas have never exceeded 200 to 300/mm³, and in any case with over 10 RBC/mm³, fluid has been recounted for WBCs after dissolving the RBCs in acid. Our counts are valid, done promptly after the taps.

We shall be mailing to you all fourteen fluids shortly, perhaps with this letter. They have been kept at 4°C since they were done. I suggest egg and animal inoculations, but have little hopes for any such attempts. Yet they should be done (? herpes, etc.), but I am most anxious to have the CSF chemistries and serology: colloidal gold sol curves, Wasserman, total protein, globulin (Pandy or some other method), chloride and sugar. I know that sugar is not valid on old fluid, if many cells are present. This has been refrigerated and has no bacteria or cells to speak of. Thus, the sugars should not be too far off and, at least, should give us a minimum level. I shall also send some of our Pandy solution for you to check on a known Pandy positive CSF, since Pandy reactions and reagents tend to be fickle. Because of the prime interest in proteins, gold sol, etc., I am addressing the fluids to Lois or to the clinical unit, but hope that you, or Anderson or French may be willing to passage them once. The shortage of tubes, etc. has made it necessary to pour off some fluid for cell counts, etc., so I hope we have not contaminated many. Fever charts reveal no temperature elevations thus far in any of the seventeen hospital patients.

We are waiting for detailed instructions on handling specimens for research neuropathology. We expect to be able to get a brain. Since many of the diseases of the corpus striatum and cerebellum require exquisite care to demonstrate their pathology, with the study of the globus pallidus, lenticular nuclei, caudate nuclei, putamen etc., and the search for demyelinating lesions, we feel that such studies should take precedence, at least in our first case, over virus isolation attempts which might, in securing the proper tissue, mutilate pathological specimens. Will you take care of securing the expert neuropathological investigations? We hope to get new supplies of fixatives from Moresby soon. In spite of the unlikelihood of any process which might be influenced by chemotherapy, we have given doses of chloramphenicol to eight patients, and will to three new patients, keeping them on a five to six day course. This includes all the children. Ascorbic acid, vitamin B complex, and folic acid supplements, together with improved diets and fish oil have been the concomitant supportive regime for these patients. Others have received one grain of phenobarbital t.i.d. without evident effects, but we are now anxious to try tranquilizers, anticonvulsants (especially tridione and phenergan), cortisone and testosterone, on purely empirical grounds in controlled series. Have you any suggestions as to trial therapeutic regimes for our consideration?

The high incidence of Sydenham's chorea in girls, the similarity of the syndrome to progressive lenticular degeneration (Wilson's disease), and familial history, such as that of the three siblings contracting the disease at about the same age, all point to a degenerative disease of the corpus striatum on a heredofamilial basis. By concentrating on the children, we may be able to exclude the possibility of previous visits to the low country, since some have never gone, and severe encephalitic illness in the past is more easily excluded, since past history is restricted at their age and more easily recalled. As I recall, the rather rapid and consistent progress to death is not characteristic of post-encephalitic Parkinsonism, while it is of the illnesses of the Wilson's disease type. Enough of the philosophizing! This is no time for arm-chair medicine on our part, but any suggestions from you or gleanings from the heavy tomes devoted to familial neurological degenerations, toxic neurological disorders, etc. will be most appreciated. We have not found Babinski or nystagmus of Friedreich's ataxia, or the cord degenerations, or usual features of disseminated sclerosis. Neither toxic reaction or deficiency, nor antecedent acute infectious disease of which this is a sequel, have yet been totally excluded.

We are telegraphing the P.H.D. for permission to construct an adequate treatment room and ward for child cases which will be a long term nursing problem, and have requested medical supplies and lab supplies for further studies and therapeutic trials. Fortunately, we are here alone, with no other Europeans as yet and, thus, have used the patrol officer's house as a treatment room for the severe patients here with us. Shortly the officer will return, however (a Mr. Baker, who is new), and we must evacuate. We have been busy lysol-ing down the house and the government office, both of which are our L.P. stations at the moment. Whatever the outcome of this study, the disease remains most devastating--and fascinating. It looks as though there will be very little to do for the patients, once neurological damage is evident; although, stories of a few recovered cases, very few, are told and are apparently valid. Since it is apparently the major cause of death, in girls at least, in childhood during the present time and for our group of

twenty-seven--almost all younger and previously healthy natives with a high probability of death--we feel that it should take precedence over most other matters in this region and hope the administration will agree and grant us the few new structures. We are in clouds most of the day and it rains fully half of each day.

Finally, we are anxiously awaiting word as to whether you will take a case or two for careful study in Melbourne, for: stereos of the skull, pneumo-encephalography, electroencephalography and thorough neurological consultation, and await word, furthermore, of any suggestions for study, treatment, and collection of specimens. Will Dr. Anderson be coming up to see any cases, and when?

Sincerely,

/s/ Carleton

Dear Carleton:

If you get this out in the jungle, good luck! I'll be waiting for you. Send the sera here -- not to KL.

Two boxes of sera arrived last month and are now frozen awaiting your arrival.

J.E.S.

16a enclosure

NIH
March 28, 1957

Dr. E. A. Hildreth
209 Maloney Clinic
Hospital of The University
of Pennsylvania
Philadelphia, Pennsylvania

Dear Dr. Hildreth:

I have just opened your letter of February 15 addressed to Dr. Carleton Gajdusek. I did this because I have today received a letter from him describing a new disease among the aborigines of New Guinea and giving his address as:

Okapa Patrol Post
Kainantu Subdistrict c/o ADO
Eastern Highlands District
Territory of New Guinea

I suspect that he will be back in several months. At that time I am sure he will be glad to advise you on matters concerning the protection of human beings against rabies.

In the meantime you may wish to get in touch with Dr. Hilary Koprowski who will assume the directorship of the Wistar Institute on May 1, 1957. Dr. Koprowski is one of the world's experts on prophylaxis against rabies.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

February 15, 1957
209 Maloney Clinic

Dr. Carleton Gajdusek
Department of Medicine
Hospital of the University of Maryland
Redwood and Greene Streets
Baltimore, Maryland

Dear Dr. Gajdusek:

At the University of Pennsylvania we are currently interested in setting up a fairly intelligent standardized procedure for the handling of individuals bitten by animals, and therefore potential rabies patients.

We are very anxious to get the opinions of those people who are actively working in the field, and who know the most about it.

In that respect, Dr. Colin McLeod suggested that I write you for any suggestions concerning this problem that you might have. I would also be most interested in any information you have concerning the newer egg type vaccines.

I know you must be quite busy, but I certainly would appreciate any information you may be able to send us.

Sincerely yours,

E.A. Hildreth, M.D.

16c enclosure

[NIH]

March 29, 1957

Dr. Marion C. Morris
Asst. Director of Professional Education
The National Foundation for Infantile Paralysis
120 Broadway
New York 5, New York

Dear Marion:

At the recent meeting of the Virus Committee, you asked me what had happened about Gajdusek since you had had no word from him since January. I have just received a letter from the wilds of New Guinea indicating that Gajdusek is now among the cannibals studying a most important new disease with neurological manifestations.

I am enclosing copies of Gajdusek's letters. I attempted to reproduce them by thermofax, but the result is almost illegible. When you have finished with the letters, please return them to me.

You will notice Gajdusek's plaintive plea for support. I would be delighted to find a means for supporting him here. In fact, we have already been negotiating about a regular staff appointment when he comes back to the United States. The main difficulty as far as we are concerned in getting any kind of support for Gajdusek is the red tape. With all the best intentions we cannot put a man on a fellowship or on a staff appointment without having a warm body and a signature. These are rather difficult to get on short notice with Gajdusek at the Okapa Patrol Post.

This is to inquire about the possibility of extending Gajdusek's fellowship from the NFIP which expired two months ago for a period of three or four months. He hopes to remain for several months in the jungle. As he points out, in his letter, he does not need any money there, but he will need some when he gets out.

If the NFIP's red tape is as bad as ours and my suggestion appears entirely impractical, please ask Tom Rivers (who is an old red tape cutter, too) if he has any ideas on the subject. If neither of you can think of anything, I'll take another crack at it.

Best wishes.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Moke...Okapa Patrol Post, E.H.
Territory of Papua and New Guinea
3 April 1957

Dear Joe:

I am writing to you just after returning from a patrol down to the southern fringe of the South Forei region, and to the Lamari River and Kukukuku and Awa linguistic areas. This little visited region, uncontrolled at its extremity and in which tribal wars, bow and arrow murders, raids and cannibalism, are still rather frequent--in fact, all three infringements of the supposed "control" have occurred here since my arrival. "Tukab", a traditional native way of throttling a sorcerer, with strangulation and stone beating to break the femur, fracture the ribs, and pound the costo-vertebral angles, is a frequent source of "emergency" medical problems, as are the wicked arrow wounds. The patrol was directed to this little known region to determine the extent south of the kuru disease, which has so occupied me and is the subject again of this note.

Here in Moke, in a mat-floor hospital which was quickly built with native materials, in which we have a microscope, hemocytometer, a host of lab reagents and equipment, and all the diagnosis instruments that such a 'bush' hospital would be expected to possess, including the ophthalmoscope and tuning forks, Dr. Zigas, the Kainantu physician and only M.D. in the Eastern Highlands who discovered the disease, and I have set up a kuru investigative station. Thus far, it is operating largely on his and my own enthusiasm and what courage he dares in leaving the European population relatively unattended while we work far out in this bush, i.e., as long as the administration which employs him will tolerate this "research" divergence.

We have now located forty-one cases of kuru, a clear cut central nervous system degenerative disease of rather rapid course, and so uniformly and progressively devastating and almost always fatal...we have examined these cases and are following them closely. Twenty-five are now in our kuru hospital--twenty-five cases of advanced Parkinsonism and cerebellar disease--thirteen in children and twelve adults. Another three children and thirteen adults are in their villages, about half of them having returned there after extensive hospital study; we intend to try to urge them back. I suspect that with thirteen child cases of basal gangliar disorder, all relatively acute and most probably doomed to fatal outcome in less than a year, and with three other children we are trying to "bribe" in, and in view of the fact that the disease is restricted to the Forei linguistic area and involves only neighboring, now intermarrying linguistic groups of Kimi and Ke'iagana in the regions directly adjacent to the Forei tribe (a population of perhaps 15,000, scattered in some of the roughest mountain jungle in the world), it is probably the highest incidence of such a disease ever recorded in any population.

We know of another forty cases, in addition to our current forty-one, who had the disease and died during the past eight months, all of whom were seen and documented by Dr. Zigas. We have accumulated histories of well over a hundred other cases that died during the past decade or so from the disease in families of our patients. It is, undoubtedly, the major disease problem among the Forei people, and beyond infancy, a period during which we have not

yet diagnosed the disease, it is perhaps the major cause of death next to warfare wounds. We now have the people's confidence; they bring patients to us and permit us to live in their villages while we hunt down cases. Since our last week of patrol we located thirteen new cases in only three clan areas with a total population of well under a thousand; further patrolling to establish the geographic extent of the illness may double the number of cases roughly. Some thirty lumbar punctures have been negative; no elevation of cells and no Pandy stronger than a rare weakly positive, in any stage of illness. There is no evidence of encephalitis now or in the past, nor any convincing acute infectious disease picture antecedent to the insidious onset of gait instability, remarkable tremor that appears more hysterical than organic, but which progresses to spasm, flexed posture, complete instability and inability to walk, loss of speech, and final and complete neurological invalidism and death, with ocular convergence, drooling, etc. late in its course. Many of our most severe cases are children of five to ten years of age, who have been ill for only three to ten months and are now near death.

Zigas and I are now preparing a paper for submission to one of the U.S. journals, with a title like "Kuru...a localized "epidemic" of chronic progressive degenerative disease of the central nervous system in children, adolescents and adults in the Eastern Highlands of Australian New Guinea". We both see clearly that unless we work out and publish our preliminary and very extensive studies, Zigas will be cheated out of anything by administrative super-structure. Secondly, I suspect a good deal of jealousy by the Australian sources shortly, as the word crops out. The fact is, that besides Zigas and myself, no other medical man in the world has investigated or seen the disease, excepting for a few administrative M.D.'s who saw some cases for a few hours, when Zigas brought them out of the region to "civilization". Hall Institute's interests are here, but no one is doing a thing and the microbiologic prospects look dimmer as I study the illness. I am shifting to further suspicions of one of the most remarkable incidences, of a whole race inflicted with a heredofamilial genetic degenerative disorder of the central nervous system--specifically of the cerebellar structure. There could be no better setting in the world for the study of such a disorder, and in spite of the tremendous odds, we really have the confidence of these 'cannibals' and 'savages'. I am rapidly learning the language, getting fine and extensive accurate family histories which are cross-checked for validity, and a better controlled epidemiology than could ever be expected in less isolated 'civilized' communities.

With this in mind, I now write to assure you that my last letter was no ruse...I have the "real thing" in my hands. I can and will continue to support myself and the project on my own funds and those that Zigas can wheedle from the Port Moresby P.H.D., now a rather complex bureaucracy, with many petty jealousies--far away from this remote mountain jungle post, but our lifeline. Will you let me know if you think even a temporary salary, which I shall throw into support of this project to pay for the axes, beads, tobacco and other trading items with which we purchase bodies (with autopsy permission) and food for our patients--a normal U.S. salary will go mighty far here--could be arranged to permit me to carry out the work for several more months, at least, long enough to watch the evolution of a number of current cases to their fatal outcome. If any added expense account could be

arranged, all the better. For \$100 worth of flown-in supplies, we hope to have a completely new building up, quite ample to house our thirty-odd patients, and another ten or twenty, all under good conditions; this would be built of largely native materials. Thus, we are really launched on the study...a second such opportunity may never present itself. I am interested to know what your general opinion may be and, particularly, since I have not yet had a reply to my first letter. Actually, for two weeks we have had no contact with the outside world and this letter is going out with Dr. Zigas on his return to Kainantu tomorrow.

Should you be able to make a grant, based on little more than your assurance of my integrity and medical judgement--I tell you Joe, this is no wild goose chase, but a really big thing. Everything in my medical training makes me confident--let me know, so that I can plan to extend my work here for at least several further months. On my own I can hold out for one or two months and still have enough to get home via Europe. But I am fully aware of the unwiseness in trying myself to be both investigator and philanthropist...enough said. I stake my entire medical reputation on this matter. In advance, however, I must tell you that we are probably dealing with a genetically determined CNS degeneration, with toxic deficiency, post-infection all failing to stand up. Since much suggests hysteria early in the disease, excepting the cases in children of five to ten years of age, I cannot get the psychosis idea out of my mind. But the advanced classical Parkinsonism and basal gangliar disorder that results in eventual death cannot easily be linked with psychosis, in spite of the role this illness plays in local sorcery, murder, warfare, etc., which gives one the consideration that it is a possible psychosis. This class of illness is not my specialty, but I can handle research on it as well as anyone. Thus, Joe, please let me know whether you can initiate or carry through even a temporary project-grant, on the promise of a paper which is already in draft form from the work. Do you not agree that such a situation is rare and not to be missed as a possible new clue in nervous system diseases, about which we know so little as yet? From here, without reliable mail or communications, I can do naught. To leave here would be fatal to the project I have fallen into, on my way to Dutch New Guinea and Malaya. I shall end up after this in Kuala Lumpur, ready to write and work further.

Autopsy material is most difficult to obtain and will require time and much persuasion, but we shall get it. We promised one brain to Melbourne, but if you can promise expert neuropathology, I shall get one off to you. Send full instructions for fixation, for removal, slicing and packing, etc., and send the necessary Customs clearances. Address any mail, telegrams, supplies or instructions to me as follows: c/o Department of Public Health, Port Moresby, Territory of Papua and New Guinea. Add: at Okapa Patrol Post, via Kainantu.

If you really think I should not abandon this matter at any cost, let me know what you know thereof, since I shall stick to it even without any grant as long as possible. Should anyone in the States be wondering of my whereabouts, let them know, since my chances of keeping up much correspondence from here on anything but kuru is most remote.

Sincerely,

/s/Carleton

[NIH]

April 9, 1957

AIR MAIL

Dr. Carleton Gajdusek
Okapa Patrol Post
Kainantu Subdistrict ADO
Eastern Highlands District
Territory of New Guinea

Dear Carleton:

We had a letter from Marion Morris saying it wasn't feasible to extend the fellowship, but Tom Rivers figured out a way to dig out some money (see my reply to him which is enclosed.) Some time, chum, you better settle down and learn how to look after yourself.

Very best.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Enclosure

[NIH]
April 9, 1957

Dr. Thomas M. Rivers
Medical Director
The National Foundation for
 Infantile Paralysis, Inc.
120 Broadway
New York 5, New York

Dear Tom:

It was good of you to phone this morning to discuss Gajdusek's problems. Of course, I was sorry to learn that it was not possible to extend Gajdusek's fellowship for several months. However, I was delighted to learn that it might be possible for you to use the administrative authority vested in the Medical Director to make available certain funds which would take care of Gajdusek during the remainder of his stay in the New Guinea jungle and permit him to buy a ticket to come home.

This is to assure you formally that we have begun negotiations with Gajdusek for employment at the NIH when he returns. Furthermore, we are most anxious to have him join our staff. The main reason for not bringing the matter to fruition is Gajdusek's casualness about such mundane affairs as jobs, money, etc. If he ever gets back here, I believe we can hold him down long enough to get the necessary signatures to put him on the payroll.

With the above assurance, may I suggest that you allocate something between \$700 and \$1000 to Gajdusek for his support for several months to continue his work on the new neurological disease (kuru) among the New Guinea cannibals, and for passage back to Washington. If you find this possible, I would suggest that you send an air mail letter to Gajdusek at:

Okapa Patrol Post
Kainantu Subdistrict ADO
Eastern Highlands District
Territory of New Guinea

Furthermore, it would be a good idea to send the money and a covering note to Sir Mac Farlane Burnet at Melbourne. Thanks a lot, Tom, for your help in getting Gajdusek out of the jungle. By this time Burnet is well aware of Gajdusek's casualness, so will probably not be surprised at such an arrangement; if necessary, he can be expected to find Gajdusek to deliver the money.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

[Moke-Okapa Patrol Post]

14 April 1957

Dear Joe:

Thank you for the copy of your letter to the NFIP (to Marion Morris). Perhaps I should have written to them myself. In any event, assure them that a series of papers on my Australian work is in press and that they can get all the reprints they need. I shall make certain that Hall Institute sends them manuscripts shortly.

Enclosed are excerpts from my last letter to Sir Mac, which will further acquaint you with our work here on kuru. I am fully at work and things are going well. I have had a bit of a spat in the mails with Sir Mac, which is concerned mostly with Australian fears of having "foreign" (i.e. American) workers studying such an exciting problem in their Territory, and their claim that we are "stealing" a problem from them, but since Vin Zigas (a full time administration medical officer) and I are the only ones working on kuru, in spite of our pleas in letter after letter for colleagues and collaborators, I have felt justified in rather forcibly stating my point. In reply, Sir Mac has been most helpful and kind in his suggestions, in spite of an initial recoil at learning that I was interested and working on a problem which he considered "his territory", for some reason. We are still hoping and begging him and the Hall group to go through with plans to come up and join us, as my letters to him--which now number five, as information-laden as the enclosed excerpts indicate--have been pleading. All seems settled now and as far as field work is concerned we are mighty busy. Eighteen cases of Wilson's disease-like 'Parkinsonism' in children, and a total of over sixty cases now in our hands, with good histories on about a hundred further documented cases, is a series not to be sneezed at. I shall eventually show you the full correspondence on the spot, now resolved, but which would have doomed our study, had I backed out.

Every bit of progress is being communicated to the Public Health Administration in Moresby and to Melbourne as we make it. Our sending two cases to Moresby was expensive (chartered plane, etc.), but a farce, since not a damned thing was really done and our patients were more neglected than they are in our bush hospital. I hesitate to say that so directly to Moresby administration or Sir Mac, but it was clearly the point...Zigas accompanied them, and what little was done, he did. Vin Zigas will be senior author of whatever we finally get out of this and, thus far, and unless our Australian collaborator-competitors come through with some help, there will be no others.

Please, Joe, ask someone in the NIH library to dig together reprints on Wilson's hepatolenticular degeneration, and any current work and theories on etiology, epidemiology, copper metabolism, ceruloplasmin, etc. in such disorders, as well as anything on current concepts and therapy of Parkinsonism-like syndromes, and send them to me at the same address you

used before, by Air Mail. Obviously, I could use some such leads here in the bush. Also, the papers on the Guam (if I recall correctly) "epidemic proportions" of amyotrophic lateral sclerosis--if that was it--for we have a somewhat similar situation, although a different degenerative CNS disorder. Any other ideas and suggestions will be immensely helpful, including any drugs you think might be critically tested in Parkinsonism, for we are really equipped to test them on one, two or three dozen cases, with controls or placebos.

Air mail reaches Kainantu, and an arduous jeep track reaches us in the bush at Moke, if we are not off on patrol. So we are in contact with the world.

Again, Joe, thank you for your help and interest. Let me know if anything comes of your note to the NFIP. Greetings to everyone in Washington, especially to Mrs. Smadel, Betsy, Nancy, and the crowd at WRAIR.

After leaving here, I am still going to Dutch New Guinea, but by that time will have exhausted any bleeding venules (I am carrying with me about 150 sent months ago from WRAIR). Should there be any real interest in specimens from Dutch New Guinea groups, send venules to me care of Public Health in Hollandia, promptly. Otherwise, I shall restrict my work to field surveys for possible future work on child growth and development.

Sincerely,

/s/ Carleton

Carleton

Okapa Patrol Post
via Kainantu
Eastern Highlands
Territory of New Guinea

P.S. Any of the drugs (or others) mentioned in my letter to Sir Mac would be most welcome (i.e. Artane, Paroidol, etc.)

19a enclosure

Excerpts:

"...cases in moderately advanced disease have gone to Moresby with Vin Zigas for one week, been seen by most medical men there, including Drs. Gunther and Scragg, and have now returned to Moke where morale is again up among our patients. Moresby was most rushed, with an overload of patients for the thoracic surgery team from Germany, and it was difficult to get things done. However, Dr. Price, in Pathology, gave great assistance and did several additional tests for us. No abnormalities of liver function were found in liver function tests. Unfortunately, EEG's, pneumoencephalograms, etc. were impossible. We shall continue to consider the possibility of sending a patient to Melbourne eventually, but can now sit quietly thinking over the matter and planning. I would still suggest your considering taking a case eventually, since there is no EEG, to my knowledge, at Fairfield and since Dr. Woods' service is so well equipped for clinical research.

At the moment we have eighteen child patients, some six of them near death, but maintained, as many neurologically deficient patients can be, on supportive measures, somewhat indefinitely. However, decubitus ulcers are defeating us in two cases at present, and we may soon have a chance at autopsy material. Whether we shall succeed in getting full autopsy permission or not is a bit uncertain. We shall do our best, at the risk of disrupting the slowly established confidence which we have gained from our other patients.

The patrolling and extensive history taking, statistical, historical and genealogical studies will take time. We shall take the liberty of sending you further specimens for clinical chemistry, and if at any time anything turns up that may offer a microbiological lead, we shall send this on to you and Anderson immediately. We have been expecting Dr. Anderson any day, but from your recent letter do not know whether to still expect him or not. Please tell him that Vin and I are anxiously anticipating his arrival.

We are trying to get our hands on Artane (trihexyphenidyl), Parsidol (diethylamino-2-propyl-1-N-phenothiazine), called Lysivane in England, and other conceivably helpful drugs for Parkinsonism, such as the trial use of BAL, calcium versenate and potassium sulfide (oral), as Cartwright et al used in trying to control copper uptake and excretion in Wilson's hepatolenticular degeneration, for clinical trial. Thus far, antihistamines, low doses of ACTH, sulfonamides, chloramphenicol, high vitamins and iron therapy, and phenobarbital have been of no effect. Dr. Scragg is sending us Tridione, Mesantoin and other anticonvulsants to use in trial, and we may get enough testosterone to try the wild lead from the expression of the disease, almost entirely in prepubertal males and in young and adult females, but very rarely in post-adolescent males.

Excerpts (continued)

...Zigas and I had in our first weeks of study in anticipation of Anderson's arrival concentrated only on gathering and ferreting out cases and observing them clinically, with emphatic attention to the child patients. The family history taking has developed into an art which involves the use of the Forei and Ke'iagana medical vocabulary and nosological classificatory system. Fortunately, all cross-checking has revealed an astounding accuracy in their diagnoses and, especially, in their spotting early kuru cases and "knowing kuru when they see it." Thus, we have been able to dig up fairly extensive family histories on many of our patients. These cannot be forced back more than a generation or two, but our concentration on child cases again has an advantage here. Old grandparents are apt to be alive and thus, when found, serve to give us the history of the paternal and maternal families of at least one, and often two generations back. In no case can we find individuals who can supply histories of events prior to their own early childhood...but the old folk do well in accurate recall during their lifetime...and cross checking of their stories usually provides support for all they report.

By this technique it has been possible to find kuru in the parents, siblings, children or aunts, uncles and cousins (by our classification) in most of our patients. Since the disease is in high incidence, this in itself would not be remarkable, but the occasional discovery of a family of from two to four siblings, all two or four of whom have died of kuru--and good verification of this story--forces genetic considerations upon us. In fact, the incidence of two to four kuru deaths in siblings in one family, with these cases developing years apart and often at very close to the same age in all children of that family, is the strongest bit of evidence for an heredofamilial ataxia that we have. In addition, there is already some tendency evident for the so-called "law of anticipation" to hold; thus, the children of an affected parent or a parent in whose family the disease has occurred, seem to have the illness at an earlier age than it appeared in the parental family.

Finally, we have now in our case hunting been patrolling far afield, and have begun to establish the limits of the disease. Nothing is as yet certain, for we have undertaken an immense job in this survey which involves prolonged monotonous discussion, interviewing, and questioning in every one of the hundred-odd villages of the affected tribal and linguistic groups--questioning which has not only been exhausting to me, but to my informants as well--but as my command of Forei and Ke'iagana begins to surpass my past smattering of them, things are working out well. It now seems evident that the spread from the Forei to Ke'iagana, Kanite, Auiana and Kimi linguistic groups, has been restricted to only those adjacent regions of probable or known intermarriage. The verification of these sharp lines of demarcation is a most important matter, for thus far we can spot no cultural epidemiological features of ecology, geology, crops, diet, etc. which could account for such a sharp demarcation, other than intermarriage.

Excerpts (continued)

Finally, I am most aware of the intense current interest in biochemical and neuro-psychiatric circles in the possible metabolic-biochemical basis for hepatolenticular degeneration which symptomatically, at least, so closely parallels kuru. If the primary defect in the disease does turn out to be the gene-determined synthetic deficit which prevents normal production of ceruloplasmin, the copper-binding globulin, then the environmental factor which might determine expression of the genetic deficit, could be sought and, perhaps, even controlled. We are trying to pursue this line of thought by planning to send food specimens, etc. to the Department of Agriculture in Moresby, where Dr. Zigas has already arranged for copper levels on blood specimens on two cases. Trace metal determinations in clinical medicine are fraught with danger and we have to run many a control before we can believe anything that turns up. Our two patients had quite normal blood copper levels, however; and we shall send more, along with controls, this time. We have, incidentally, found no evidence for liver disease of any sort, as yet.

We have now located over 60 active cases of kuru...and none of these patients have yet died. Of these sixty cases carefully and fully studied, forty had lumbar punctures.

[NIH]
April 22, 1957

AIR MAIL

Dr. Carleton Gajdusek
Okapa Patrol Post
Kainantu Subdistrict
Eastern Highlands District
Territory of New Guinea

Dear Carleton:

At the Federated Societies meetings in Chicago last week, I ran into Tom Rivers who said that he thought your NFIP Fellowship would be extended for a couple of months. You will recall in an earlier letter I indicated that he had dug up some money from the NFIP Medical Director's fund to buy you a ticket and tide you over. In Chicago he said that the Fellowship Committee, after he had tentatively allocated the money, decided that it would be simpler for them to take his Director's funds allocation and to extend the fellowship. All of which points up again that red tape is the same damn color no matter what the large organization. You can just be thankful that Tom is a good red tape cutter.

Dr. Greenfield is the visiting investigator here at the Institute of Neurological Diseases and Blindness and Dr. Bailey, the Director of the Institute, asked Greenfield to put together directions for the collection of CNS and other autopsy material from a case of Kuru in case you are lucky enough to get a post mortem. These directions are enclosed.

Best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

20a enclosure

Dr. Joseph Smadel

Recommendations for the removal and fixation of the brain (with reference to New Guinea disease).

Scalp incision from ear to ear over the vertex coming down a short distance behind the ears. Peel the scalp back.

Cranium. A horizontal saw-cut round the skull from forehead to occiput is usual. Rather better is a wide V shaped cut 1) from above the hairline on the forehead to near the ears, 2) from the external occipital protuberance to the same point near the ears.

Dura mater incised and cut along external to the sagittal sinus on both sides. Cut falx anteriorly and posteriorly. Cut tentorium cerebelli. Remove the brain by cutting the cranial nerves and arteries. Cut at the medulla-spinal level as low as possible, preferably from both sides with scissors. Remove the dura and falx, and preserve them. Pass a string under the basilar artery, and by means of this suspend the brain in:

Formalin	750 ml
Na Cl	60-75 grm.
Water	5-6 litres

A longitudinal incision through the middle third of the corpus callosum along with an incision through the infundibulum allows formalin to pass into the ventricles and helps fixation of the basal ganglia. Leave in this fixing solution for not less than three weeks, in a container with a lid to prevent evaporation of formalin. The formalin solution should be changed after two or three days. In my opinion the quantity of formalin is important point. A large brain requires more than a small one. It is a common rule for fixing tissues with 10% formalin saline, that the amount of fixing fluid should be ten times the bulk of the tissue. This rule is difficult to apply to the brain, which may have a bulk of 1500 ml. Using stronger formalin up to 15% instead of 10% and changing after two or three days, avoids this difficulty. We have found 15% formalin gives generally better and more certain fixation than 10%. More than 1% salt also does no harm, and may prevent swelling. For histological work some degree of shrinkage does not matter. When well fixed, the brain is not likely to deteriorate, if it is wrapped in one or two layers of cotton soaked in the formalin solution, put in a cellophane bag, sealed to prevent escape of fluid and packed in an air-tight can. Early and thorough fixation is all important. No fixation can remedy the effects of post-mortem autolysis, or the cavitation which may be caused after death by growth of bacilli of the gangrene group.

J. Godwin Greenfield

20b enclosure

[National Foundation for
Infantile Paralysis]
April 23, 1957

Joseph E. Smadel, M.D.
Associate Director
National Institutes of Health
Department of Health, Education, and Welfare
Bethesda, Maryland

Dear Joe:

I am returning your correspondence from Dr. Gajdusek as you requested. I understand that you have heard or will hear from Dr. Rivers and hope the arrangements will be satisfactory.

Sincerely yours,

Marion C. Morris, Ph.D.
Assistant Director of
Professional Education

Enc: 1

[NIH]

May 1, 1957

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea

Dear Carleton:

Enclosed are the notes from Dr. Greenfield on how to obtain and preserve CNS tissue. Another page containing similar advice on the same subject is also enclosed. This came through Dr. Bailey, the Director of NINDB who apparently decided that Greenfield's notes would not be available in time. The two sets of information are somewhat different, but in many respects they supplement one another.

Very best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Enclosures

PROTOCOL FOR REMOVAL AND FIXING BRAINS UNDER JUNGLE CONDITIONS

Remove brain in the ordinary way, i.e., coronal scalp incision from ear to ear, sawing round the skull horizontally above the ears, removing calvaria. The dura is then cut out round below the skull, the falx divided anteriorly in the depths of the great longitudinal fissure and is reflected backwards, cutting the veins and adhesions as one proceeds. The frontal lobes are then gently raised with one hand and the optic nerves cut, also the outer cranial nerves as they become visible (the olfactory bulbs are freed from the cribriform plate, first of all).

The tantorium cerebelli is now cut on either side with the point of a sharp knife, taking care not to damage the underlying cerebellum. The incision starts at the edge of the incisura and passes outwards and backwards on each side so that the anterior part of the tantorium is separated from the petrous part of the temporal bone. The cranial nerves emerging from the brainstem are now divided. Finally the cervical spinal cord is cut through as low as possible with a long knife passed through the foramen magnum. Do not pull too much on the brainstem during this procedure and try not to cut the medulla obliquely instead of the cord. The whole brain and cerebellum can now be allowed to fall backwards out of the skull into the hands of the operator.

Fixation: Unless post mortem can be done very soon after death, it will be helpful to inject the skull with strong formalin solution (equal parts of commercial formaldehyde (40%) and normal saline). The needle is passed through the inner canthi of each eye and formalin injected into the middle fossa. Also a cisternal puncture is advisable, CSF sucked out and the strong formalin injected. This will help to harden the brain and make removal easier. Keep the dura and its sinuses and fix with the brain. When the brain has been removed a thin thread is passed under the basilar artery and the brain suspended by this so that it floats submerged in a large container (e.g., a bucket or flour-bin) filled with 10% formal-saline solution (Formaldehyde 10 cc, normal saline 90 cc). A small incision through the front of the corpus callosum may be made so that better penetration of the ventricles can be brought about. Fix for 3 weeks or longer, changing the solution twice.

The brain should be packed whole, wrapped in layers of lint or wool saturated with formal saline solution and sealed in a cellophane bag. This, in turn, is well packed in cotton wool and put in a large, strong tin or the container provided. The packing should be tight enough to prevent movement of the brain within the tin.

This procedure should give excellent preservation for a child's brain. With a large adult brain it will be advisable to cut the brain coronally through the base of the frontal lobes in front of the optic chiasma after a fortnight in the fixative and to complete fixation for another fortnight in fresh 10% solution. The central white matter will be reached better by the fluid if this is done. About 6 liters of the formal saline solution should be used in any case as a minimum.

[NIH]
[mid-May 1957]

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu,
New Guinea)

Dear Carleton:

Dr. Bailey has just sent me some summary material with bibliographies dealing with Wilson's disease. I hasten to forward these to you.

Very best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Attachments

22a enclosure

MEMORANDUM

To: J.E. Smadel
Associate Director (Intramural Affairs)

From: P. Bailey
Director, NINDB

Subject: Summary and treatment of Wilson's disease

Date: May 7, 1957

Thank you for the interesting communication from Dr. Gajdusek.

I am attaching two short summaries recently made on Wilson's disease and its treatment, which you might like to photostat and forward to Dr. Gajdusek.

Pearce Bailey, M.D.

[7 May 1957]

WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

Wilson's disease is a familial disease usually starting in young adults and showing signs and symptoms of degeneration of the cerebral cortex, basal ganglia, and cerebellum. There is a positive family history in about 50 per cent of the cases.

In addition to the central nervous system involvement, there may be evidence of liver diseases ranging from mild changes in the laboratory tests to severe liver failure.^{47,48}

It has been recognized for many years that there are changes in copper metabolism in Wilson's disease. These have been important in suggesting a source of treatment in this previously untreatable condition, as well as in aiding in differentiating between mild cases of Wilson's disease, in which the liver involvement is the most obvious clinical feature, and cirrhosis of the liver. In Wilson's disease there is an increase in copper in the tissues and apparently in the central nervous system as well. However, the serum copper level is low, and there is an increased excretion in the urine. In cirrhosis there may be an increase in urine copper excretion, but there is also an increase in serum copper. The source of copper which is deposited in the central nervous system may be from increased absorption from the intestinal tract.⁴⁹

There is an increase in amino acid excretion⁵⁰ in patients with Wilson's disease. This may be present even if liver disease is not demonstrated.

TREATMENT. - In view of this abnormality in copper metabolism and the effects of British anti-lewisite in the treatment of heavy metal intoxication, BAL was tried in the treatment of this condition.^{49,51-54} Several programs have been outlined.⁵⁵ One calls for the use of 4 ml. of 5 per cent solution of BAL subcutaneously four times a day for the first day and then 4 ml. of the same solution twice a day for two days and once a day for the next three days. This is repeated in two-week intervals, and as many as four courses are given.

Another treatment calls ^{56,57} for the use of a total of 2.2 Gm. of BAL in 10 per cent peanut oil solution given in doses of 100 mg. twice a day for eleven days. This course is repeated about four times within a six-month period.

Side effects of nausea and pain at site of injection have been noted, but these are not sufficient reasons to discontinue treatment.

It must not be thought that the treatment will bring about a dramatic change. Although improvement has been noted by nearly all investigators with few exceptions,⁵⁸ it may not be retained^{59,60} and

the downhill course may continue. However, the treatment is successful in reversing or arresting the course in many instances.

Because of the ability of ionic exchange resins to remove sodium in patients with cardiac disease, it was tried in Wilson's disease^{47,61} for the removal of copper. Sodium polystyrene sulfonate can be given in doses of 15 Gm. three times a day; definite clinical improvement has been noted. This is associated with an increase in excretion of copper in the stools. Patients became refractory after a period of time. However, discontinuing the treatment for periods of one or two weeks will overcome this difficulty.⁶¹

In view of the use of Versene in the treatment of lead intoxication, it has been tried also in Wilson's disease with improvement noted in one case.⁶¹ ACTH produced an increase in tremor and is apparently of little⁶¹ or no value.

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Wilson's Disease and Chelating Agents

Wilson's Disease (hepatolenticular degeneration) is characterized by an increased amount of "free" copper in the serum and spinal fluid, deposition of copper in the body tissues (especially liver and brain), and an increased urinary excretion of copper. Ceruloplasmin, a copper-binding serum protein in the alpha-2 globulin fraction, is decreased to very low levels; thus copper is present in the free form and cannot be bound to proteins.

Copper in the serum, tissues, and urine can be analysed chemically and its metabolism can be followed in vivo by use of radioactive Cu^{64} . Ceruloplasmin can be extracted physically and inferences as to its amount can be made through analysis of serum copper as well as through a dye test using N, N-dimethyl-paraphenylenediamine. (Science, 125:117, 1957).

An objective in the treatment of patients with hepatolenticular degeneration is to reduce the amount of copper in the serum and the body tissues. A low-copper diet and absorption of copper from the gut by use of oral potassium sulphide or carbo-resin can reduce the amount getting into the circulation.

Attempts to bind the serum and tissue copper into a complex that can be excreted in the urine have involved the parenteral use of 2, 3-dimercaptopropanol (BAL), intravenous calcium disodium ethylenediamine tetracetic acid (calcium versenate), and, most recently, oral penicillamine (a breakdown product of penicillin). Each has been successful both in chemical result and clinical improvement, although the latter cannot be sustained. These substances are "chelating agents"; they are organic molecules with the ability to form internal complexes with metals.

In this Center, there is a patient who could not dress himself nor feed himself and who had extreme difficulty in walking because of the involuntary movements. After a course of penicillamine, he could do these things well except for slight difficulty in certain skills of eating. Whether this improvement was due to the drug or to a natural remission has not as yet been ascertained.

The chelating agents show promise in being able to aid in the elimination of excessive copper to some extent. However, the essential step will be to prevent the abnormal accumulation of copper from occurring, but as yet it cannot be done.

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W. King Engel

Pintogori, Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea

Dear Joe,

I thank you for all your efforts and successes on my behalf, and I assure you that I am fully at work on kuru, perhaps the most important epidemiological problem in the world at the moment; in fact, it potentially holds many leads. It is certainly the most fascinating that could be visualized in any part of the world.

Enclosed are further carbons which will add new information to what you now know. I write at the moment to let you know that we have had a kuru death and a complete autopsy. I did it at 2 a.m., during a howling storm, in a native hut, by lantern light, and sectioned the brain without a brain knife. But the brain in 10% formal saline is off to Melbourne for neuropathology, along with pieces of all organs I sampled, fixed both in Zenker's and 10% formal saline. We are sending to you by air freight three small tubes containing fixed tissue specimens in 10% formalin in saline (10% formaldehyde); in addition, there are three small tubes with Zenker's fixed tissue. Sorting the mixed tissue out, once fixed, is fraught with some uncertainty, and I may have been wrong in identifying them. However, here is a list of what I think you are getting. Formaldehyde fixed tissue in 10% formaldehyde in Ringer's for the first 64 hours, then in 10% formaldehyde saline. Tissues assorted between the three bottles (fixative identifiable as numbers A, B and C (the smell will do)): liver, kidney, muscle and the fascia of anterior abdominal wall, lung, pancreas, aortic wall, section of cervical cord, ovary, a piece of cerebral cortex, and the spleen. There may be some adrenal and pancreas and heart tissue somewhere in these formaldehyde fixed specimens; the pituitary in its entirety is off to Melbourne.

Zenker's fixed tissue--in Zenker's with 5% glacial acetic acid added for thirty-six hours--washed with q.l hourly changes for thirty-six hours, placed in 50% ethanol for twenty-four hours, and then transferred to 70% ethanol, in which they were shipped (no iodine added yet to remove the excessive Zenker's). Bottle #1 contains: ovary, pancreas, meninges and heart. Bottle #2 contains: heart, aortic wall and valves, kidney, ?adrenal, and ovary. Bottle #3 contains kidney, lung, spleen and liver. Every bit of pathology which can be thought up would be much appreciated, although grossly we found no abnormalities. The enclosed carbon copy of our clinical record--incidentally, we are keeping similar clinical records on some sixty patients with this "Parkinsonism" or, rather kuru, which is a disease in itself--will give you some details about this child patient who died of typical kuru. The next autopsy I shall try to get to you in entirety, rather than to Melbourne. The first goes off to the Royal Melbourne Hospital.

Joe, there has been much politics and jealousy, coupled with the study of kuru by Vin and myself. No other investigator has even looked at the illness, until S.G. Anderson paid us a half-hour political visit, designed mostly to smooth over controversies with the administration which Sir Mac had stirred up, by noting that it was a bit unfortunate that Australian workers did not have

this study in their hands. However, Sir Mac was 'told-off' in a letter by me in reply to his notes, and since then has been most cooperative, helpful, and offered every assistance possible. In fact, I hear on the Australian National Broadcasting network about the great team of experts at work on this scourge. All this while I am struggling to get Gram's stains working, Leishman's stains prepared, and our Pandey solution standardized, without a hand of help from anyone thus far, but Vin Zigas, who is stationed in Kainantu and makes the risky mountain track jeep trail here on a day's trip at every possible moment, and spends every bit of time he can with me. I have a native hospital, built with the help of the patrol officer, the only other European here in the area of 30,000 native population, much of which is 'uncontrolled'. "Tukabu", the ritual formalized murders, keeps him busy when he is not dealing with cargo cults in the more sophisticated of our Forei and Kimi and Auiana neighbors. The natives have been fine friends, and have thus far cooperated well. We have twenty-two cases now in the hospital, over half of them children, and I shall regularly be bringing in some of the forty-odd others back for follow-up. They all seem to be following much the same rapidly progressive course, with certain few notable exceptions, and the uniformity of the syndrome is remarkable.

Heavy metal toxicity is a thing we are pursuing, and a clinical trial of BAL is underway. I have not yet seen any response to antibiotics, phenobarbital, benadryl or pyribenzamine, cortisone acetate, ACTH, aspirin or vitamin preparations. We have had a remarkable chance to evaluate these potential therapies, but our patients have degenerated while on high doses of each of these. If you can get any of the tranquilizers to me--ample dosage and literature for treatment of a half dozen or dozen cases--or more particularly, any of the new anti-Parkinsonism drugs, I should be most anxious to try them. Here, I have no source of supply, although the administration which is basing its highly publicized intensive investigation of the scourge "by a great team of experts", 100% of which Vin and I do, is really supplying us with about whatever we need. I have the native-material house nearly finished and will be able to move our lumbar puncture, autopsy and urinalysis and reagent preparations off the kiap's, i.e., the local patrol officer's, dining table shortly. In addition, I am sending you under separate cover a stack of carbon copies of some of our case records, minus the temperature and treatment charts, which I do not have in duplicate. These you may study, but please hang on to them for me.

I have a letter from Geoff Edsall informing me that my manuscripts will be awaiting me in Kuala Lumpur. It will be at least a month or two before I can wind up the current phase of kuru research and head, via Dutch New Guinea and Borneo, for Malaya. Kuru is a most difficult thing to abandon...it is too good a problem. A few letters have reached me to let me know that the AICF test paper is now out in Nature, and that my pneumocystis paper is out in Pediatrics. The series of definitive papers on AICF reactions will probably appear in the Annals of Internal Medicine, an unfortunate result of coupling the experimental paper with a follow-up clinical coordination, which would not fit well into experimental journals. However, I think our work is good and will stand up.

May I hear from you again, and any ideas and suggestions will be most appreciated? No news as yet from your neuropathology experts?

Sincerely,

/s/ Carleton

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea
28 May 1957

Dear Joe:

Kuru is becoming ever more interesting and baffling. I am discontinuing cortisone acetate on five moderately severe to severe cases in children, having reached toxic levels over a course of two weeks without a sign of improvement in the moon-faced subjects. Another six, five of them children, are on high doses of BAL, the therapy having been conducted along with as controlled urine collection routine as the windy, stormy mountaintop we inhabit would permit. We managed to collect specimens in clean enamel kidney dishes, washed with catchment water out-of-doors to avoid dust and smoke from all the houses, including our hospital ward, and with a minimum of debris entering the specimens. Some were collected in chemically clean glassware, and all have been transferred to either vacuumatic bleeding venules or other similarly clean containers. The serial specimens collected during the first 18 to 24 hours of high BAL doses after an initial specimen should settle the matter of real copper intoxication, mercury intoxication and other possible heavy metal poisoning, which must be considered in this disease. I am sending one set of these serial urine specimens to Moresby for copper levels by the agricultural chemistry lab. However, I am rushing this note to you to learn if you could dig up mercury, manganese and similar heavy metal levels, since heavy metal intoxication is the major possibility we must now rule in or out--probably out--all possible metals which might be the offending agent, by even the remotest possibility. Can you find someone interested enough in this really fascinating matter to give us a hand?

I shall send you for storage, at least, along with the pathological specimens and the brain, a set of serial urines on such BAL clinical trials. They are precious specimens and have cost us heavily in time and effort to obtain under these primitive conditions, where even the suspicion of sorcery worked on body parts or excreta is a great hindrance. We would like any and every study which neuropathologists and biochemists can think of. Copper is indicated because of the close neurological parallel between Wilson's disease symptomatology and our disease. Mercury, I read, can in certain forms of chronic poisoning, give rise to neurological tremors. Manganese is said to do the same in some animals, I am told. Thus, we are grasping at every straw.

New cases have now developed under our eyes, all our 60 to 70-odd study cases are slowly, some rapidly, deteriorating, and we have raised the number of cases we have ferreted out of the Forei's 8,000 to 10,000 population to 75 active cases. In the past six months there have probably been 100 deaths from kuru in the 15,000 population...estimate...affected by kuru and another 100 active cases, at least, are present (we have our hands on 75). These 100 can be expected to be dead in six to twelve months, with some exceptions (probably not over 20% still alive by then). Thus, some 1% of the population, or more, is now dying per year of kuru, and from our epidemiology, it appears that at least as many have died yearly over the past

five, perhaps ten, years. Finally, some centers have up to 6 to 10% of the population now sick with active progressing disease, and many centers can attribute fully one half of all deaths to kuru in any of the past five years. Could any more astounding and remarkable picture be found anywhere?

The picture is too uniform and its progression so classical that it is hard to believe. We have taken 8mm cine films and three reels (not four, as noted in my last letter) are off to you, whereas, I hope to airmail out with this letter another three twenty-five foot rolls of 8mm cine Kodachrome. These are the property of Dr. Smythe, who is visiting to give us a hand temporarily. It is a chance for us to get films of many of our best patients, along with the peripheral activities and ethnology of this remarkable population. Please do all you can to get at least one good copy of the films run off for file awaiting my return for editing. Already it will be possible for you to spot the salient features of kuru, if the film is at all well taken. We have filmed many patients and demonstrated some of their instability, ataxia, grinning, emotionalism and tremors. These films, coupled with our earlier ones which we shall dig up and send to you, will offer a chance of seeing the very same patients at various stages of their illness. I think they will be far more important than the rabies film I brought back from Iran. Finally, I would very much like to get more usable, more manipulative 16mm film, but have not yet found the means.

We may send some tapes of recordings of the foolish speech, giggling, and chatter of some patients, along with the control patients' speech hesitancy, blurring and slurring examples, with records of local traditional music. I can borrow these from our recorder, which equipment is far from perfect, if you can have as high fidelity copies made for us as the tapes themselves warrant.

Should you be able to get an airmail shipment of venules off to me, especially those adequate for trace metal studies on their contents, i.e. chemically cleaned interiors, I shall do all in my power to get blood, tissue, etc. off to you for file. At the moment, liver and renal function tests, serology, etc., rather crude, but the best we can get, are being sent off to Moresby and Melbourne.

Again, many thanks, Joe.

Sincerely,

/s/ Carleton

Pintogori, Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea

Late May 1957

Dear Joe,

I received your notes on the treatment of Wilson's disease by Dr. P. Bailey, and the two notes on brain fixation by Greenfield and Bailey on brain post mortems. We have, as you may have already learned from my recent note, had one post mortem on kuru now, and the brain is off to Melbourne. I would just as soon send the second brain off to you. This first brain was taken one hour after death and fixed after sectioning, rather sloppy, I fear, in 10% formal Ringer's and transferred in 10% formal saline on the third day. It may give us some answers. My last note told you of extensive pathological materials off to you; I hope the small pieces are adequate for some studies. We have had several (eight cases) blood copper determinations already done--at a well equipped agricultural research lab--and they are about normal, although higher than in a control series we sent with them. They were not ceruloplasmin studies, but rather, total whole blood or total serum copper levels. Other copper studies are now planned and BAL treatment will now be started after seeing that even cortisone has been without effects.

New cases are always turning up. There have been other deaths, but we could not get posts. I have my hands on a few others and will try my best to get posts, but these are not people you can push. They are proud and have their own ideas, which are most intelligent, and although they have conceded that I can cure their meningitis and pneumonia, they have decided that this magic is too strong for me and that my prolonging life by treating and controlling decubitus ulcers is no blessing at all. They want to die at home, and once fully incapacitated, they want to die as quickly as possible. With such apparently hopeless neurological disease, you cannot blame them. Since we have done lumbar punctures on over fifty--repeatedly on some--and taken 30ml blood specimens, collected urine and blood for CBC's, and sedimentation rates frequently, and loaded them with painful shots (everything from crude liver and cortisone to parenteral antibiotics) without any effect--and they know it--I have only more respect for their 'hands off' attitude. But, to humor me and repay my many miles of mountain climbing to track them down, they haul the litters over miles of cliff-faced and precipitous jungle slopes to bring the patients in for another shot at our therapeutic trials and experimental poking...I admire and respect them thoroughly.

Thank you for all the help; keep sending literature, new ideas, suggestions and anything else you can think of. Could eating prussic acid in uncooked manioc cause anything like this? They have now manioc as an introduced crop from the neighboring tribes for the past decade, just when kuru got bad. Any drugs, special equipment, etc. which may be of use would be of help. The usual drugs, antibiotics and standard supplies, I have plenty of. Can you handle photographs; could you get me cine equipment (16mm) and film on loan for a fine kuru film? It would be really impressive. I shall send you black and white still negatives.

Sincerely,

/s/ Carleton

Pintogori, Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea

Dear Joe,

Developments are rapid. We had a second kuru death, a classical case in a middle-aged woman who had been long under our observation. Just after receiving your brain handling instructions, we varied our procedure and did not slice the brain, but fixed it whole in 15% formol saline, with opening of the ventricles. Brain, pituitary, cauda equina (we cut too low for much of the lumbar cord in our rush), bone cervical cord and almost every organ of the body is now in ample slices, or in its entirety in 10% formal saline, except for the CNS in 15% formol saline. We shall change later to 10% formal saline, wrap in gauze and cotton, and try to get all this off to you. We even have a sample of the formol saline for trace-metal controls, in case you can use the tissue for this purpose. I shall keep the controls here in our mountain jungle highland lab, pending word from you re the several problems. We have excellent air service by the bush pilots who connect with Qantas in Lae, and from there there is a once every two weeks' service to KLM in Hollandia, and thence via Europe around the world to you; perhaps better, twice or three times weekly from Lae to Sydney, and then via PAA to you. I can now send this all right and anticipate no trouble. This is fixed non-infectious tissue. However, could you clear with the local PAA and have them clear with Sydney's Qantas and with Qantas in Lae (in the Territory of New Guinea), and with Qantas in Port Moresby (Papua) that I am authorized to send--as I usually do anyway, without such preliminary preparations and, incidentally get away with--shipments to you by Convert to U.S. Government Bill of Lading? What I am really driving at is for PAA to get Qantas locally, i.e. in Lae and Moresby, to know that they can accept such shipments and should push them rapidly forward. I suspect we shall get them off without trouble, but Lae is a long way off, and Vin may go all the way in to be sure things work O.K. Kuru brains are not a commodity on the open market, nor will they ever be; we are lucky to get any. The material is really precious and we need every assurance possible that it will 1) get through, and 2) find those interested and prepared to study it. Sorry for all these technicalities.

We have seventy kuru patients being intensively followed, and we are now preparing a preliminary note on this exciting disease, because we have finally awakened to the fact that we have sent off enough reports and data for a dozen reports to be written by those who have never looked at the disease. Our epidemiology is by no means complete, and we are still in the dark as to etiology. Patients are walking in and deteriorating so rapidly and in so stereotyped a fashion, that it is hardly believable.

We are going to try to dig up our good 8mm cine film of kuru, which we loaned to visitors and never got back, and I want to send it to you for duplication. It is a really precious document, I am told by those who have seen it. We were visited by Dr. William Smythe, from Rabaul, who has been shooting more 8mm for us. I am taking the liberty of sending you four 25 foot rolls of 8mm cine Kodachrome, undeveloped, three taken here in Moke and one enroute here by Dr. Smythe. Three have a good deal of kuru in them, which should be easily recognized. Danger: one "longlong" (village idiot) doing a foolish dance is also on the last of the four films, and is not to be mistaken for kuru. If you

can get at least one, better two, copies of these made and the originals eventually returned by airmail to Dr. Zigas, Medical Officer, Kainantu, E.H., Territory of New Guinea, we shall have had the complete use of this cine photograph which is irreplaceable if it comes out O.K. In addition, I should like to have your permission to carry out the same scheme with future cine film by visitors. Furthermore, if any good 16mm equipment can be dug up, as I wildly suggested in my last letter, I should still be most interested, for there is not much better a thing to film in cine in the modern medical world than kuru. Naturally, everyone would like to get their hands on kuru brains; we were lucky to get two and may get further ones, but our ex-cannibals (and not 'ex') do not like the idea of opening the head, although other dismemberment does not seem to perturb them...death, however, away from their remote villages does! We both, Vin and I, feel that you at the NIH could do more than anyone else on the pathologic material and, thus, are sending the major portion of this, our second post, on to you. The first brain at Melbourne is from the same child, whose portions of viscera we sent off to you. The spleen in that lad was really small. The spleen in the women was unusually small and shrunken, and nothing else abnormal was noted except for 1) a very fatty heart with thin myocardium and much fat; and 2) a peculiar subpial arachnoid fluid, ?exudate collection which appeared blood-stained and may well have been the brain removal trauma, but which was over one cerebellar hemisphere and extended down along the cerebellar stalk into the angle between the cerebellum and midbrain. I think this is an artifact we produced, but it did look funny, and since we are dealing with a tremor-ataxia disease, perhaps the most dramatic such in existence, it behooves one to look hard at the cerebellar surface and subarachnoid space.

Trace metal studies in the chemistry lab or the Department of Agriculture in Port Moresby gave slightly high serum coppers, but not dramatically so, and not even higher than some controls. More are being done, and the accompanying letter to Dr. Price will keep you informed about what we are trying to get done this way. However, just how accurate and how extensive such trace metal studies can be, I cannot evaluate from here, and this brain or the next may be the last we ever get. So please ask your neuropathologists and chemists to think about what might be done. I still think kuru is one of the most important problems in existence in medical research, for it has all the earmarks of one that may give a real lead into chronic degenerative neurological diseases. Trace metal toxicity is only our current craze--it must be fully investigated--but we still have family histories of the disease in well over half the cases and have even seen multiple family cases. It rarely lasts over a year in the village, from onset to death. Fully developed kuru is invariably fatal, all the natives say, and it certainly seems to be; early kuru ataxia and tremors occasionally regress and disappear, and we have seen this occur. Thus far, this has only been in hysterical temperamental women, who may well have been well, but mimicking early kuru in their hysteria. Since kuru is a major, perhaps the major, death threat, magic threat, and cause for vendetta killings in the tribes today, such hysterical mimicry would not be remarkable. Certainly, most of our seventy current cases seem doomed, and our child cases have advanced before our eyes, in spite of every type of treatment. BAL will now be started as soon as we get a gang of them back to normal from the moon fascies and other cortisone toxic effects, which an intense and ineffectual course of cortisone acetate produced in them as their kuru progressed.

I shall shortly send you my black and white film negatives on kuru, in the hope that you can get some printing and enlarging for a file that will eventually be used in the publications. I shall catalogue and describe all film frames on each negative on a note to you. Please let me know, Joe, if I am over-burdening your wide interests in medical problems by inflicting kuru on you this way. I really think it deserves every bit of emphasis I am giving it. Should you be

able to see our ward filled with "epidemic Wilson's-Parkinsonism", which is what this is clinically, but probably not pathologically or etiologically, I think you would fully agree. A native-material house is rapidly nearing completion, with a 24 x 24 foot room and table lining all four walls for our specimens, the slides, papers, records, etc., and ample pacing room. Thus, we and our visitors will be able to eat on a table without post mortem specimens at the one end, and be able to do lumbar punctures at night on the other than autopsy tea-lab-typewriting-bench-emergency surgery table, that must be cleared for meals three times a day. Our kuru cases have been moved into a majestic new hospital that we have built by cooperative efforts of some one thousand Forei-Kimi-Keiagana natives, and it is quite a cozy place in the stormy down-pour which beats on our mountaintop.

Sincerely,

/s/ Carleton

26a enclosure

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of New Guinea

Dr. A.V.G. Price
Public Health Laboratory
PORT MORESBY

Dear Dr. Price,

Vin Zigas and I are ever more grateful to you for all of your help. We have read over the results of copper levels on our patients and on the controls, and also the controls from Ela Beach, which you added to the study. It appears that if copper metabolism is involved in Kuru it will be a most subtle matter requiring extensive controls and, eventually, probably ceruloplasmin studies, etc. However, we think every line of possible approach should be exploited, and we ask you to continue requesting copper studies for us. In addition, is there any chance that manganese and other trace metal studies might be done, or is copper the only one set up in Moresby at the moment?

Gray Anderson explained that Mr. Holden at Hall Institute would only be prepared for copper--perhaps also manganese--but hardly any others. He offered to check for us with CSIRO laboratories in Melbourne to see what they might do. Thus, should any of these new specimens which we are now transmitting to you not be exhausted by your copper and other studies, will you please freeze them down in chemically clean glassware adequate for trace metal studies, in order that they may be used in the future should we be able to line up other trace metal studies? Again I am sorry to place so many burdens and problems upon you. We have received so much real help from you already, we are tempted to repeatedly call upon you for more.

A second Kuru patient has died and we managed to get a post mortem examination. Again the brain and viscera were grossly normal. Spleen rather small and shrunken. We have taken extensive organ specimens into 10% formaldehyde and also into the Zenkers-Acetic Acid which you have furnished to us. These we shall keep here a while, washing, etc., and eventually send specimens and brain off. Would you be willing to again receive portions of various tissues for further histopathology, as we have already without warning sent to you such specimens from our first autopsy?

The shipment now being sent to you is summarized on the accompanying sheet. It includes blood specimens in sterile, chemically clean vacuumatic ampules, those used previously and described to you, from ADULT KURU patients, all with typical advanced disease, and from some normal Forei control subjects from the same villages. These are collected for copper level studies along with other trace metal studies if they can possibly be done. Furthermore, we should like

luetic serology, liver function tests, and any renal function tests (NPN or BUN, etc.) possible along with total protein and any protein partitions possible, all as previously, which the volume of the specimens will permit and which your time and facilities can provide. Again, such huge orders and requests are embarrassing for us to make of you, as we have previously indicated, we both know full well what an immense job such laboratory studies can be. However, these are things we cannot do here in Okapa Patrol Post and they need doing. Kuru remains the same unsolved problem and we are trying everything for "leads".

Along with the blood specimens is a bottle of bile aspirated by syringe from the gall bladder at post mortem. Any chemical and trace metal studies possible on this would be of value. In addition we are sending 4 other tubes which each contain slivers of autopsy-collected organs: spleen, liver, kidney and psoas muscle respectively. These have been placed into bottles which were chemically cleaned for trace metal studies in Melbourne...and thus should satisfy the chemists...if they can manage to use such material. Since no fixative or solutions have been added these specimens have been kept frozen in our ice chamber and in a Kainantu deep freeze as much of the time as possible...for they were NOT collected under totally sterile conditions. We hope they reach you in usable form. Certainly copper levels and ANY OTHER studies possible would be of great interest on these specimens. We are not likely to get much further such material!!

Having requested such an absurd amount of work, we might as well go on. Could you make up further Zenkers solution and send it to us along with acetic acid? We do expect at least one more autopsy--perhaps two--shortly, and we have used fixative in vast quantities, taking rather extensive collections of every organ in the body in our last two posts.

Could you ask the chemists, Mr. Easeden and Mr. Southern, to supply us with chemically cleaned glassware for trace metal studies adequate for collecting further pathological specimens, further blood specimens, and, in particular, for supplying urine specimens, etc. which we shall collect in connection with BAL (British Anti-Lewisite) therapeutic trials which we shall now begin to conduct. Incidentally, cortisone carried to fully toxic levels failed to alter the course or severity of the disease.

Since BAL can stimulate the excretion of a wide range of heavy metals deposited in the body, the BAL-trial specimens will be particularly valuable for copper studies as well as others...and we thus request in advance that aliquots be set aside for these other studies.

Should you or your colleagues, Dr. Price, have any suggestions to make to us, please may we have them. We are seeking advice and discussion from every side, for while we have this opportunity to study kuru under fairly good conditions, it will be foolish to have overlooked observations which could

easily have been made or experiments which could easily now be conducted. It will not be for much longer that we can keep some 70-odd KURU patients under our thumbs, and the local Forei will not welcome being guinea pigs for much longer--unless we can provide evidence that we have something to offer them--which is unlikely.

Please tell Mr. Easeden and Mr. Southern that we have in mind writing to them personally with our gratitude and thanks for all their endeavour...but thus far it is all we can do getting these notes off on secondary specimens we send out to you, to Melbourne, and elsewhere.

Again accept our thanks for your enthusiastic cooperation.

Sincerely,

D.C. Gajdusek

V. Zigas

SPECIMENS FOR CHEMISTRY AND SEROLOGY STUDIES AND FOR TRACE METAL
DETERMINATION ON KURU PATIENTS

BLOOD SPECIMENS ON ADULT KURU PATIENTS (in chemically clean glassware):

Collected 25/5/57

IAMOGI
AVETO
EWANTA
ASOMEIA
TARANTO
YOBUIUTA
IA'I

CONTROL SPECIMENS COLLECTED AT SAME TIME FROM ADULT NORMAL FOREIGN INDIVIDUALS:

ANUNTA	Female (mother of Yani)	c. 35 yrs. old	from KAMATA
MASONA	Female	c. 33 yrs. old	from KEIFU
NUMBOLETE	Male	c. 20-25 yrs. old	from OKASA
ERIKREPME	Female	c. 30-35 yrs. old	from MOKE

PATHOLOGICAL SPECIMENS: fresh tissue put into chemically clean bottles without solution of any sort added. No fixative. Keep frozen or refrigerated, since not collected under sterile precautions. Collected 1-2 hours post mortem.

Bile
Spleen
Liver
Kidney
Psoas muscle

all from patient YO'EIA (Joeia)

NIH

May 29, 1957

Air Mail

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Okapa Patrol Post
via Kainantu
Eastern Highlands
Territory of New Guinea

Dear Carleton:

Your long letter (date not given, presumably about 22 May) describing recent developments in kuru and the autopsy arrived yesterday. Today, the tin box containing the fixed material, reached here in good condition. I shall consult with Dr. Bailey and others regarding who might study most profitably this valuable pathological material. I will write you a letter shortly with answers to some of your questions. I am glad to know that your two papers have just come out in Nature and Pediatrics. I'll look them up.

Enclosed are carbon copies of letters from Tom Rivers to you and to Burnet. Please write dear Tom a good letter, thanking him for his fine efforts in getting you \$1000. Best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Enclosures

27a enclosure

NIH
May 29, 1957

Dr. Thomas M. Rivers
The National Foundation for
 Infantile Paralysis, Inc.
301 East 42nd Street
New York 17, New York

Dear Tom:

I was delighted with your note of the 21st concerning
copies of your letters to Gajdusek and Burnet. Many thanks
for all of your help.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director
National Institutes of Health

27b enclosure

[National Foundation for
Infantile Paralysis]
May 21, 1957

Joseph E. Smadel, M.D.
Associate Director
National Institutes of Health
Public Health Service
Bethesda 14, Maryland

Dear Joe:

I am sending copies of letters to Dr. Carleton Gajdusek and to Sir MacFarlane Burnet. I am sorry that I have been so slow in getting the check off but we have been in the process of moving and I was out of town for ten days.

Sincerely yours,

Thomas M. Rivers, M.D.
Medical Director

Enclosures

Pintogori
 Okapa Patrol Post
 via Kainantu, Eastern Highlands
 Territory of New Guinea
 [May 30, 1957]

Dr. Joseph E. Smadel, Associate Director
 National Institutes of Health
 Bethesda, Maryland
 U.S.A.

Dear Joe,

Enclosed is a summary of a large shipment of urine specimens which is fully explained on the accompanying sheets. As far as trace metal possibilities, copper is one which Wilson's disease brings to mind and mercury is listed as another which causes basal gangliar type tremors in some forms of chronic poisoning. Can your associates suggest any other leads, for it is a bit unbelievable to find 1-2% --in some nuclei of population up to 5-10%-- of a population sick at the current time with this astonishing, rapidly progressive, fatal disease. Cortisone therapy did NOTHING. Well being was enhanced, perhaps, but tremors, ataxia and incoordination were unchanged. BAL therapy is now instituted, using: "Injection of B.A.L.; B.P.-Oily Injection of Dimercaprol" prepared by Boots Pure Drug Co. Ltd., Nottingham, England.

The enclosed sheet summarizes our tropical bush attempt at 24-hour urine collections under hellish conditions for any such controlled experiment. However, negative results would be rather conclusive, and our correlations are as accurate and carefully made as can ever be done under such conditions. Any help with any and every trace metal, urine amino acids, and any other studies you can do would be much appreciated. The complete autopsy materials, formalin-fixed brain (whole) with formal-fixed and Zenkers-fixed tissues, will be off to you shortly. Any histochemistry for heavy metal deposits, etc., would be much appreciated. Furthermore, control specimens of the formal saline used in fixing tissues are sent for blank analyses. Neuropathology, whether completely negative or with interesting positive findings, may considerably clarify the kuru matter. All other pathology will be of value, as well. Yaws is present, but we have a number of positive SSF Wassermans without any other sign of CSF Treponematosi...On New Guinea patients with their gamma globulin derangements, this may mean nothing. But, can silver impregnations for spirochete also be made? Some 60-odd kuru spinal fluids have thus far been negative. We shall send you some CSF for trace metal studies later.

Thank you for all the help and interest.

Sincerely,

/s/ Carleton

Carleton

P.S. Tables summarize only first two days of BAL treatment. Patients are continued on the same dose for another 3 days or so. Dose is high, since patients are mostly thin and frail...and, you will note, most are small children!

Please let me know about the cine-films when you finally see them. This is a really good problem, Joe, and I hope you someday get to see it. A wild---really wild---suggestion. Would anyone in the USA be interested in CNS diseases, especially the degenerative ones: Parkinsonism, Wilson's disease, etc., be interested enough to undertake the wild venture of bringing a set of these kuru cases to the NIH for real study??? Nothing short of this will ever settle the issue, and our child-patients could be managed well. The trauma to the natives of bringing two to Moresby--where less was done than we do here in the bush--could not be exceeded by New York or Washington; these fellows adapt quickly to airplanes, Jeeps, jets, etc.! Australia has not really offered us anything in investigating a few cases in their centers, other than Fairfield Hospital which is NOT equipped, and funds are hardly available. I just pass this wild suggestion on; I could easily get a set of mildly ill but rapidly progressing child-cases with interpreters and guardians off to you if and when funds and administrative authority were cleared, and more might be settled that way than by thousands and thousands spent in "field ventures". This IS a new disease Joe, and an important one. I have been flatly rejected on plenty of these "wild" schemes, but when I see how millions of dollars are spent on far more hare-brained schemes, I consider them worth making. Enough for now.

/s/ Carleton

SERIAL URINE SPECIMENS ON BAL-TREATED KURU PATIENTS

First specimens in each series collected before first dose of BAL and series consists of all subsequent urine specs. for first 24 hours or more after initiation of high-dosage therapy.

Volume of each specimen and time dosage record for each patient will be supplied under separate cover.

Specimens are labeled serially with Roman numerals.

Containers: All specimens are in vacuumatic bleeding venules empty controls of which can be furnished if these prove to be trace-metal contaminated. There are four exceptions, however. These exceptions are:

YANI I.....in a medium-sized (15ml) trace-metal free screw-topped bottle.

YANI II.....in a small (10ml) trace-metal free screw-topped bottle.

YANI IV.....in a large (25ml) chemically cleaned but not necessarily trace-metal free bottle...an empty control of which can be supplied.

TASI KO I...in a small (10ml) trace-metal free screw-topped bottle.

COLLECTION: Specimens were collected in trace-metal free--to start with--enameled kidney dishes which could not be washed between voidings because we have no trace-metal free water. (These were prepared and packed in Australia). It was absolutely impossible to keep out all traces of dust, vegetation and other wind and draught-borne debris during the 24 hour period of collection...and it will always be here in Moke short of catheterization, which Forei resistance prohibits...but the maximum possible effort has been exerted to keep out extraneous matter. It has not always been successful.

Since smoke of our wood-fire heated native-material hospital wards, wind and dust when collections are made out of doors, and falling debris from native roofs when collections are made under any sort of native roof cannot be fully avoided, trace-metal contaminations may have occurred. However, any consistently high trace metal in the urine or, more especially, any

consistent rise in a trace metal content upon BAL therapy would be an important lead, while failure to find any excessive mercury, copper, lead, manganese or other trace metals in any of the specimens would rather conclusively eliminate poisoning with such elements as a possible etiology of kuru.

Control urine specimens can easily be supplied and will arrive in our next shipment of specimens together with specimens from further BAL-treated cases. BAL dosage scale is high !

Amino acid patterns and any other possible studies on these urines which might help give some lead on kuru would be much appreciated. No urinary abnormality has been thus far found in kuru.

SPECIMENS:

NATA: I	220 ml	TASIKO: I	20 ml	ATONA: I	390 ml
II	55	II	110	II	185
III	345	III	55	III	220
IV	285	IV	70	IV	290
V	150	V	125	V	190
ARANAKA: I	140 ml	YANI: I	40 ml	AVETO: I	110 ml
II	230	II	80	II	40
III	70	III	8	III	55
		IV	30	IV	30
		V	40	V	28
		VI	70		
EWANTA: I	100 ml	IAMOGI: I	160 ml		
II	12	II	50 ml		
III	50				
IV	80				

BAL TREATMENT SUMMARY

ARANAKA: Male, 7 years old

27 May 1957

1530	URINE I - 140 ml
1532	BAL 1 - 2.0 ml (100 mgm)
1932	BAL 2 - 2.0 ml (100 mgm)
1945	URINE II - 230 ml
2345	BAL 3 - 2.0 ml (100 mgm)

Had marked increase in tremors and convulsive-like exaggeration of kuru-repetitive movements after BAL 2 (2000-2200) -

28 May 1957

0900	URINE III - 70 ml
1000	BAL 1 - 2.0 ml
1730	BAL 2 - 2.0 ml

YANI: Male, 4 years old

27 May 1957

1100	URINE I - 40 ml
1101	BAL 1 - 1.0 ml (50 mgm)
1500	BAL 2 - 1.0 ml (50 mgm)
1600	URINE II - 80 ml
1800	URINE III - 8 ml
1900	BAL 3 - 1.0 ml (50 mgm)
1945	URINE IV - 30 ml
2200	URINE V - 40 ml

28 May 1957

1000	BAL 1 - 1.0 ml (50 mgm)
1730	BAL 2 - 1.0 ml (50 mgm)
1800	URINE VI - 70 ml

AVETO: Female, 45 years old

28 May 1957

1100	URINE I - 110 ml
1130	BAL 1 - 4.0 ml (200 mgm)
1330	URINE II - 40 ml
1600	URINE III - 55 ml
1600	BAL 2 - 4.0 ml (200 mgm)
1830	URINE IV - 30 ml
2000	BAL 3 - 4.0 ml (200 mgm)

29 May 1957

0700	URINE V - 28 ml
1000	BAL 1 - 4.0 ml (200 mgm)
1700	BAL 2 - 4.0 ml (200 mgm)

EWANTA: Female, 20 years old

28 May 1957

1115 URINE I - 100 ml
1130 BAL 1 - 4.0 ml (200 mgm)
1400 URINE II - 12 ml (contaminated with much debris--sedimented out)
1600 BAL 2 - 4.0 ml (200 mgm)
1630 URINE III - 50 ml
2000 BAL 3 - 4.0 ml (200 mgm)

29 May 1957

0700 URINE IV - 80 ml
1000 BAL 1 - 4.0 ml
1700 BAL 2 - 4.0 ml

IAMOGI: Male, 17 years old

28 May 1957

1600 URINE I - 160 ml

29 May 1957

1200 URINE II - 50 ml (then BAL started. Other specimens to follow!)

NATA: Female, 8 years old

27 May 1957

1200 URINE I - 220 ml
1201 BAL 1 - 2.0 ml (100 mgm)
1600 URINE II - 55 ml
1601 BAL 2 - 2.0 ml (100 mgm)
1845 URINE III - 345 ml
2001 BAL 3 - 2.0 ml (100 mgm)
2145 URINE IV - 285 ml

28 May 1957

1000 BAL 1 - 2.0 ml (100 mgm)
1445 URINE V - 150 ml
1730 BAL 2 - 2.0 ml (100 mgm)

TASIKO: Female, 6 years old

27 May 1957

1530 URINE I - 20 ml
1531 BAL 1 - 2.0 ml (100 mgm)
1700 URINE II - 110 ml
1845 URINE III - 55 ml
1931 BAL 2 - 2.0 ml (100 mgm)
2145 URINE IV - 70 ml
2231 BAL 3 - 1.5 ml (75 mgm)

TASIKO: continued

28 May 1957

0830	URINE V - 125 ml
1000	BAL 1 - 2.0 ml (100 mgm)
1900	BAL 2 - 2.0 ml (100 mgm)

ATONA: Female, 7 years old

27 May 1957

1145	URINE I - 390 ml
1146	BAL 1 - 2.0 ml (100 mgm)
1215	URINE II - 185 ml
1546	BAL 2 - 2.0 ml (100 mgm)
1946	BAL 3 - 2.0 ml (100 mgm)
2030	URINE III - 220 ml
2345	URINE IV - 290 ml

28 May 1957

0800	URINE V - 190 ml
1000	BAL 1 - 2.0 ml (100 mgm)
1730	BAL 2 - 2.0 ml (100 mgm)

[Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea]
June 7, 1957

Dear Joe:

Enclosed you will find a manuscript of a paper we are preparing as a preliminary note for a "general" journal, such as ~~Nature~~, since it is now obvious that our great mass of data and records will require a set of papers which will be months, perhaps years, in preparation. Kuru remains fully in our hands; we have had no one else make the arduous journey in to see it, but we have, as you can see, interested a number of others in peripheral problems. It remains every bit as good a problem as originally, and our findings have provided a great mass of negatives. We are about where we were with EHF all the time--perhaps even more in the dark--and all our patients continue to get worse and we are now poised before a rapid series of deaths in six to twelve of our patients. Whether we shall get any posts or not, I cannot judge, but the formal-saline fixed brain and cord and pituitary, and all viscera and Zenkers-fixed portions of tissues on our second complete autopsy, are all off to you along with this letter. Keep an eye out for them and please direct them to as good a histopathologist and neuropathologist as you can, for you may never again get a kuru brain in the U.S., unless we are very lucky.

I am out of containers and venules as of today, for we are sending two dozen further kuru blood specimens to Melbourne, from where the sera will eventually go on to you in the U.S. The exciting alpha and beta globulin matters are being pursued, but, as you may know, globulins in all New Guinea natives are haywire, with no relation whatsoever to our temperate-zone American normal "standards." However, the beta rise is so spectacular, approaching a macroglobulinemia, that it must be further pursued.

We have our hands full with twenty-four cases on dilantin, tri-dione and cortisone--various groups at the moment--and we are waiting to see whether intensive BAL treatment of ten has done any good or not.

Please keep me informed of the receipt of any of the pathological specimens, etc. Did the first set of fixed tissues (the brain of which went to Melbourne) ever reach you, and did you get the BAL urines?

The enclosed correspondence to Sir Mac will let you know a bit more of what we are up to. He himself has not seen kuru. Anderson, who was interested in it, came in for a few hours while in New Guinea, but is not really working on it. However, others in Moresby and Melbourne are giving us a mighty hand, and Anderson is lining up much of what we request with the labs that can handle it. However, nothing is as urgently needed as good study of the brains and other tissues. Please let us know what turns up. Enclosed, also, you will find the carbon copy of the history of the deceased patient whose tissues you are getting. Please file it away for me. There is much added data on her, which I do not have in duplicate.

Sincerely,

/s/ Carleton

Pintogori
Okapa Patrol Post
via Kainautu Eastern Highlands
Territory of New Guinea

29a enclosure

4 June 1957

Dear Sir Mac and Gray,

I have been so busy that it has been impossible to keep you as well informed as I should like to have done. Slowly, but surely, we have dug up new cases and persuaded the old known cases into Pintogori for complete study. Furthermore, I have extended the intensity of our clinical studies and, I hope, perspicacity. Complete blood counts with good staining of films finally worked out and are being done and have been done routinely on over thirty of our patients, a job requiring days of work. Nothing remarkable in the RBC, WBC, differentials or hemoglobins has yet been found. I shall send stained films to Melbourne shortly for whatever rechecking Dave Cowling or others with good hematological background can arrange.

We have used up every ampule of BAL that Anderson brought with him in treating ten patients, mostly children, on a single five to six day course of high doses of BAL. I received, in addition to the fine abstract summaries of dose schedules which Gray brought, a complete review of current methods of treating Wilson's disease, with such other methods in addition to BAL as chelating agents: penicillamine, calcium versenate, etc., oral potassium sulfide, etc., prepared by Pearce Bailey of the U.S. Department of Health. Thus, we used probably a better controlled BAL regimen and previous workers have been able to use a bit more of it. Urine collections were made on all but two of the ten patients, these two being incontinent and the specimens being always missed. Catheterization was out because 1) we have only one catheter and 2) the local gossip ensuing from the use of the catheter would have been such as to jeopardize our rapport with the natives. Urine specimens collected in every available container, which was or 'might be' chemically clear, were sent on for copper levels and mercury levels, I hope, to Moresby, with instructions that aliquots thereof be sent to you in Melbourne to supplement the specimens we sent to you. If anyone at CSIRO or elsewhere can run spectrographic analyses for any excess of heavy metal or trace metal, we should be most appreciative. Mercury, copper and manganese come to mind first, mercury, since some forms of chronic mercury poisoning do result in basal-gangliar type tremors, I read.

Nothing unusual in local diet yet gives us any leads. I have caught many natives eating a particularly strong form of raw ginger, but am assured that everywhere in the territory this occurs without kuru ensuing. Cortisone, carried to toxic levels, readjusted and now maintained on high moon-fascies producing doses, has not helped any of the five child patients a particle. BAL cannot yet be evaluated. No change occurred during its administration. I am now running a group on dilantin, which finally arrived, and shall soon start with tridione. One man, an adult male patient, is now on good doses of testosterone. I would like to know something about maximal safe testosterone doses and can find nothing here in the literature available...can you help me? The hunch is that since adult males are particularly saved, perhaps the male sex hormone has something to do with it, and we can more easily boost a male who has the disease to normal male testosterone levels than a female.

Thus, clinical study, which at the moment must be intense since patients are on near toxic levels of cortisone, delta-1-hydrocortisone and agranulocytosis-dangerous tridione and dilantin (which is also renowned for stomatitis and other reactions). Local Forei resistance to hospitalization is increasing;

they know damn well that we do nothing for the disease, but prolong its misery by supportive measures, and they are anxious to return to their technique of starvation and neglect in darkness, which ends in a speedy exodus once the illness is truly incapacitating. We have had several more deaths in patients in our 'series' of seventy-five-odd severe cases. From one adult whom we had followed closely, we were able to get a complete autopsy. Tissues are in fixative and being kept pending adequate containers and firm fixation, but will then be sent on for histopathology. The case showed no gross lesions at all; the spleen was noticeably small and shrunken, and sectioning all organs grossly revealed nothing unusual. We are still trying to get further brains and will do our best. I have asked Moresby for more BAL, for we have not a speck left for further trials or, more important, for follow-up courses, should any effects at all be seen from the first course on our ten BAL treated cases.

Epidemiology is continuing. I have tracked kuru into Usurufa linguistic area, but again in the Forei-border where Forei-Usurufa intermarriage occurs. We sent a set of chemically clean trace metal-free containers of bottled CSF's to Moresby for trace metals. I trust you will get aliquots for mercury, lead, manganese, etc. studies.

PINTOGORI
OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of New Guinea
4 June 1957

Dear Sir Mac and Gray,

I ran out of paper on an Aerogramme, so I continue my last letter on a new sheet.

In a note from Tom Rivers I learn that he has sent a check for \$1000 U.S. made out to me from the National Foundation for Infantile Paralysis (which is an extension grant they have given me) to you. Will you please have your secretary post it to me registered mail c/o Dr. Vin Zigas, Kainantu, by air mail? I can manage to handle it here. This is not to be confused with the \$1000 additional grant to the Hall Institute to cover some of the expenses of my last year of work with you. I never learned whether Hughesi had arranged fully for it or not.

Thank you, Sir Mac, for your kind letter of 24th of May. It was a great relief to Vin and me to learn that the first brain had arrived safely and was already in Dr. Hicks' hands. A note from Simmons informs me that he has done an immense lot of blood group genetic work on our specimens and I believe that it will all fall very well in place once we can sort out the records and results, for the genetic stock of these people may turn out to be a key question. I shall shortly send new batches of blood for further red cell, hemoglobin, and serological study along with new CSFs. Since the vacuumatic bleeding venules we use are apparently satisfactory for trace metal work--as the Moresby copper determinations using them seem to demonstrate--(and, in addition, I can always supply a few controls which are empty), I wish to request any other work on trace metals which anyone in Melbourne can manage to do. The serum-blood specimens should, if handled properly for trace metal work once the venules are opened, be adequate for trace mercury, zinc, copper, manganese, etc. In addition, they may be OK for amino acid studies to be correlated on any urine amino acid chromatography you can do. Can any of the "BAL collection series" of urine specimens which you received be used for urine amino acid chromatography?

Dr. Price has done masterly work in getting together with the Agricultural chemists--blood copper determinations done for us. Nothing remarkable has turned up as yet.

I am very much intrigued by the N-N-dimethyl-paraphenylenediamine dye test estimates of ceruloplasmin which I have heard of but the reference I have not yet seen (SCIENCE 125: 117, 1957). Can someone look it up for us and determine whether there is anything therein which we might undertake?

Certainly trace metals must be pursued to the fullest, since they do offer a distinct possibility. However, I am beginning to become more and more skeptical that we shall find anything. New dietary leads may turn up. Thus far raw manioc and raw ginger are the only two I can find that are at all remarkable....and old Territorials assure me that this is a pan-Territorial trait, not particularly Forei.

The full epidemiological survey from which we shall establish definitive statistics as to incidence and death rates from kuru is being slowly pushed forward, and the final delimitation of the zone of occurrence of kuru is being attempted. I shall shortly be devoting much attention to patrols designed to settle these unfinished matters. Thereafter, I think we shall have reached the phase of diminishing returns--and the Forei the limit of their patience and toleration--and at that point I shall sit down and start analysis of our records and charts prior to leaving the highlands. I shall bring everything to such a state that Vin can follow all of our patients easily by a visit every 3 months or so to the region and the use of his doctor-bois to roam the hills, and in such order that a return in 12-18 months could be brief and yet definitive for determining what had happened to the natural history of kuru in the interval.

Please greet any of my friends you may meet in Geneva. I am still planning to stop in Dutch New Guinea, Borneo, and Malaya and to then cross the Middle East to Europe, and I still hope to be there by autumn and back in the U.S. before winter.

Please ask the new librarian to send on reprints of the Pediatrics and the Nature papers to me when they arrive, and inform her that a paper on Cape York Aborigines has been submitted to the American Journal of Physical Anthropology. If the Institute wants copies thereof--Simmons, Graydon and I have written it and I am listed as of Hall Institute, where I did the work--and to include it in its bibliography, I shall be happy. Simmons can make any necessary arrangements. The New Britain-New Guinea survey paper will shortly be off also.

I have not yet fully digested Paper II of the AICF series, but brief study leaves me quite satisfied. I hope we meet with no further editorial difficulties. Please ask Ian to send on to me any further editorial communications promptly. I should like to be able to look over page or galley proofs--of the first and second papers--but there is no need to hold things up for this. If such proofs can be sent to me, any real errors I might discover would still be handled by cable.

A third paper--based on the reams of yet unassimilated data we accumulated--is being written now, and I shall submit it to you once an adequate draft is ready.

Again I thank you both for all your help and assistance. Tell Gray that I shall see that all Institute needles and instruments are shipped back when I

pull out. In the meanwhile, a new supply of chemically clean, trace-metal free bottles and needles would be a most helpful addition to our supplies. I have nothing to put autopsy materials into for such determinations. In fact, if you can design trace metal free--or at least "controlled" formalin (10% formol saline)--and/or ethanol for proper preservation of tissues which may still be used for trace metal studies I should very much like these. We cannot get away from metal tin contained formaldehyde and other fixatives here in the bush. Trace metal free bottles--empty and sterile, would be of help for further blood specimens and CSFs.

Sorry, once again, for so many requests. If I ever get to Lufa, I shall try to see the tremor cases Ian has dug up. He is now on patrol.

Sincerely,

/s/ Carleton

P.S. Your letter announcing the arrival of the check from the Foundation reached me after this was written. Thank you, Sir Mac, for all of the administrative details which you have been saddled with and cared for for me. I am deeply grateful. Please send the check on to me at this address where I can easily negotiate it through the mails.

May you have a fine trip through Europe. I trust the meetings will be interesting and I hope that you may find it possible to return through the States once again. If so, I may possibly be there already.

Lois has voiced repeatedly an interest in seeing New Guinea, and I suggested that she use her time off to come up for a visit here if it could conveniently fall into the period when we still had accommodations and facilities available. This is now and for the next month or two. I hope that this might coincide with a natural slump in your lab work coincident with your leaving for Europe. Certainly, I should like to see her again--a decided understatement.

[NIH]
June 25, 1957

AIR MAIL

Dear Carleton:

In case I have not previously done so, I hereby acknowledge receipt of a large batch of urines, another autopsy, several letters including the case history of the patient from whom the second autopsy material was obtained, and finally, the draft of your paper on KURU. It is a very nice paper, not only good but interesting. I hope you have already sent it off to the Journal. Why NATURE? Why not LANCET?

Mr. Wipf, Administrative Officer, National Institute of Neurological Diseases and Blindness, has brought together material for photographing the KURU patients. The list is attached. It will go off within the next day or so. Look, chum, I practically had to swear to Wipf that I would be responsible for all this stuff. Either you come home with it or leave your head in New Guinea. We have received six rolls of color film from you to date. These have been sent out for development and for preparation of two color dupes. When all of it is returned, I will file under appropriate conditions the original film. Then a number of us here will run off one of the copies to view it as it may be helpful in getting ideas about KURU. The second dupe will be sent to you promptly by air mail.

I am leaving on the fourth of July for the Fourth International Poliomyelitis Congress in Geneva and will be back about August 1st. The way things shape up now, I may be one of a number of Americans who go to the Ninth Pacific Science Congress at Bangkok which goes on for several weeks in late November and early December. Just what days during this period I shall be in Bangkok is still unsettled.

If my general calculations are correct, you will probably be out of New Guinea about September or October and will spend a month or so in Kuala Lumpur. Frankly, I don't see how you are going to do all this traveling on the \$1,000 Tom Rivers got for you, but you manage to get around on relatively small amounts. It is certain, however, that this particular check is the last one, so you better get back to the United States before you run out of money. I really don't see much point in your spending two months in Kuala Lumpur, but if you do and still have any money left, you might go to Bangkok for the Congress.

-2-

Dr. Baker got some information for you on chronic cyanide poisoning.
Copies of this are enclosed.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. Carleton Gajdusek
Pintogori
Okapa Patrol Post
via Kainantu, Eastern Highlands
TERRITORY OF NEW GUINEA

Enclosures

Material received and ready to ship to Dr. Gajdusek by air express:

1. Camera, motion picture, 16 mm. for 100-foot roll film, Bolex H-16 with f 1.9, 1 inch reflex lens.
2. Case, camera, Bolex H-1.
3. Tripod, heavy duty, quick-set with elevator.
4. Weston Master III. Exposure Meter with case.
5. Eight, 100-foot rolls of 16 mm. Kodachrome color film (Daylight Type).
6. Four, 100-foot rolls of 16 mm. Tri-X Reversal black and white film for varying conditions of daylight.
7. Polyethylene bags and silica gel.

NOTE: All film by Eastman-Kodak. Vacutainers should arrive very soon and will be shipped immediately. Above camera for 100-foot roll film strongly recommended in preference to Bell-Howell with 50 feet magazine by two NIH photographers and one other photographer for use in climatic conditions such as those of New Guinea.

To guard against moisture and dampness, material will be packed in polyethylene bags with silica gel. An additional supply of polyethylene bags and silica gel will be included in the shipment to Dr. Gajdusek.

[Okapa Patrol Post
via Kainantu
Eastern Highlands
Territory of Papua and New Guinea]
June 29, 1957

Dear Joe:

I have just returned from twenty days of patrolling over some rugged, little-known country, tracking down kuru. I managed to delineate the western boundary of the kuru region and to find where kuru came into the Kimi neighbors of the Fore, and where it did not. It extends only along the Fore-Kimi boundary, and in some cases can be traced into the Kimi Kuru-free regions following the marriage of a Fore girl into the Kimi, the disease occurring in her, years after she left the Fore kuru-region and started residence in the previously kuru-free Kimi region. This border area is the most profitable region for kuru study, for kuru is an isolated event in a rare family here, while in the central Fore it is the major cause of all deaths. However, in spite of more and more clinching evidence for a genetic pattern, I found a few "red herrings"--as a Kimi girl from a supposedly kuru-free Kimi community getting kuru after coming to the Fore kuru region. For one such case, there are dozens of the genetic-suggesting others, but the one "red herring" is enough for thought.

We now have over a hundred active kuru cases, and our cases are starting to die off rapidly. We get autopsies only with difficulty, but now have two more brains on hand, both first fixed in 15% formaldehyde and then transferred to 10%, in which they are being shipped to you. Case histories are being sent to you on these two deaths, both in patients we have followed and treated extensively. One, in a small girl; another, in a middle-aged woman. Both were classical kuru. Thus, these will be the second and third kuru brains sent to you. Neuropathologists in Melbourne kept telling me that perfused brains were essential, and that without perfusing through the carotid arteries and circle of Willis, the specimens would be inadequate. If this is so, please let me know, send me full instructions and any necessary canulae, etc. We will have plenty more brains coming, I think, and we can definitely follow through much more complex procedures. I am now getting ready to try to get a brain in trace metal-free formaldehyde and trace metal-free containers. Can you supply any proper plastic containers or bags for such a brain? We can get distilled water and trace metal-free HCHO flown in to us from Moresby and Australia. The girl, whose brain is coming, died while I was out on patrol, and a native medical assistant followed our instructions and obtained it and dropped it into previously prepared fixative. The second, on the woman, I obtained with Vin Zigas, and we did a complete post--finding nothing unusual, except again the same slight exudate-like material over the cerebellum, which I am not sure is not from brain removal trauma. In any event, the full brain and meninges are fixed and sent to you, and samples of liver, kidney, pituitary, adrenal, stomach, intestine, abdominal wall muscle, and spleen and uterus are also included. All are HCHO-fixed, with the exception of a small bit of Zenkers' fixed tissue, so labelled.

Once we leave here, kuru pathological material will be no more, and, thus, I beg that you consult everyone who might have a bright idea. I fully suspect no pathology to be found--as is the case in many a toxic or degenerative neurological disorder--and thus the most subtle and original techniques are indicated. One brain, sent to Melbourne, sectioned here, has revealed nothing thus far, but ? reduced number of Purkinje cells in the cerebellum. That our patients are rapidly dying of a rapidly fatal progressive neurological degeneration is certain, and some one hundred are now in our hands. We have tracked down histories of some five hundred such deaths in recent years and have only just begun. Furthermore, from my last patrol, we tracked down a high incidence of kuru to near the Papuan border into very little-known country. We are about to launch searching patrols into the uncontrolled Kukukuku regions which border on high incidence Fore regions and to try to establish the furthest southern extent. That no yet discernible ethnic or ecological feature, other than marriage with Fore, seems to characterize the kuru limit, seems more and more certain. We have, I suspect, the highest incidence of a genetic neurological disturbance ever seen in a large population...it is a mighty striking disease, as you must have already seen, if the films are at all intelligible.

Please keep any notes I have jotted on the film packs with the respective films. We have no other record. However, I think that Vin and I can reconstruct a real film story from recall when we get the films for editing with you. We already have pictures of the progressive stage of illness in several individual patients, and when we can dig up our first film and get it to you, you will have early films of many patients who have subsequently died, and were filmed in their progression. Two films (cine) are going out with this letter; one has several new cases in children and follow-up pictures on several old cases. Another has kuru cases--follow-ups--and a good deal of panorama of the kuru country in which the boundary between kuru region and non-kuru region can be shown later. I think, Joe, that this ciné material, if it is O.K., may be one of the most valuable documents of the entire work. Thus, I burden you with it. Enclosed with this letter is a black and white 35 mm film No. 1. With the ciné films come black and white 35 mm film No. 2 and 3; these are already developed and form an important part of kuru documentation. I have several hundred kodachromes on file already, and I shall ask my brother to bring you a set he has, which I sent home to have developed. Please keep them in sequence and in your hands or his. The black and whites I would very much appreciate having printed. If some convenient size--say, postcard size or any standard small enlargements--could be made of each frame on the three films, and filed serially with you in a kuru file, I should be most pleased. There is no need to send copies to me...just have a kuru file established, if you believe it justified, as I certainly do. In addition, certain pictures are obviously of importance and usable already in publications that I hope to start working on. Therefore, I should like to request two copies of enlargements suitable for publication to be made of the special frames, designated on one of the enclosed sheets. One enlargement is to be kept in your file, and the other sent to me for selection for the papers; a set of papers is in preparation and manuscripts will go off to you when they are ready. Something like 8X10, or near it, is perhaps best for the enlargements.

One enclosed list documents all frames on the three black and white films. Another lists only those desired in duplicate large sized blowups, one for us here and one for you.

Thank you, Joe, for all of your encouragement and support. We are really getting things done. Vin and I have the entire matter on our hands, but we are getting support in equipment and special tests from Moresby and Melbourne as we request it. The draft of the preliminary report I have sent to you. Many additions and improvements can now be made, but I am awaiting your comments. Lois Larkin, Sir Mac's technician who did all the AICF work with me, will be co-author of our third paper on this; she is up here "on her vacation" with us and with her help we are really going to get our Kuru Center moving full speed during the next few weeks before launching off on patrols again. BAL and cortisone did not help dramatically, but to decide whether they help a bit is most difficult. Patients survive months when well supported in our kuru ward, and go off to die in the village only days or a few weeks after our temporary discharge. To differentiate between the specific effect of drugs, and that of pure nursing support, is a most subtle matter.

I am ever more convinced that kuru is one of the most exciting and fascinating medical problems unsolved today, and one which offers to medicine many an insight, especially in this modern age of fear of gene-induced dangers to populations...for where in the world is another population so threatened by a lethal set of genes?? Obviously, I am still thinking genetically, but remain open to toxic, infectious and other possibilities, if they can be found. No luck yet.

We are isolated, and every word from you is a great encouragement. Here we cannot possibly handle these many technical matters which I presume to thrust upon you. I think kuru is interesting and important enough, Joe, to warrant this intrusion. I am sending a copy of this to Tom Rivers, along with a copy of the draft of the "preliminary report", with a note of thanks to him for the check. I am living frugally here, but without salary I should have been stranded when I pull out, were it not for this help. Thanks.

I have not yet seen the Pediatrics article, but the Nature article has come up and I am most satisfied. The correspondence response is very satisfying, but I only wish I could stir up the U.S. editors on the two definitive papers which should be out and are not yet even accepted: AMA Archives of Internal Medicine--I almost feel like taking it out of their hands and sending it to Clinical Investigation or Journal of Experimental Medicine, for I know the work is good.

Sincerely,

/s/ Carleton

Carleton

[NIH]
July 7, 1957

Dear Dr. Gajdusek:

Dr. Smadel asked that I write to you for him since he and Dr. Shannon have left for Europe.

The Editor of Science called regarding your manuscript entitled "Kuru...A Localized 'Epidemic' of Chronic Progressive Degenerative Disease of the Central Nervous System in Child, Adolescent, and Adult Natives of the Eastern Highlands of Australian New Guinea". He feels, and Dr. Smadel agrees, that the paper is more suitable for publication in a medical journal than in Science. The style of the manuscript is that usually found for articles in medical journals, rather than in such a journal as Science. In order to save time, Dr. Smadel has taken the liberty of submitting your manuscript to the New England Journal of Medicine for publication. This Journal, as you know, is one of the top medical journals with a wide circulation. Other possibilities considered were the Journal of Tropical Diseases or some journal in the field of neurology. When the more detailed paper is ready for publication a neurology journal might be the preferred choice for publication.

The camera, film and bleeding venules are on their way to you. We have prints made of the movie film and will send you copies under separate cover. We will store the negatives and an edited copy of each print under appropriate conditions here at NIH. The National Institute of Neurological Diseases and Blindness is working up the tissues and urine samples which we received from you. We will keep you informed of the developments as they arise.

Sincerely yours,

Carl G. Baker, M.D.
Assistant to the Associate
Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu, New Guinea)

[NIH]

[July 1957]

Dear Dr. Garland:

The enclosed manuscript by Drs. D.C. Gajdusek and V. Zigas, entitled, "Kuru...A Localized 'Epidemic' of Chronic Progressive Degenerative Disease of the Central Nervous System in Child, Adolescent, and Adult Natives of the Eastern Highlands of Australian New Guinea," is submitted for your consideration for publication in the New England Journal of Medicine. This newly discovered disease will be of interest, I believe, to many of the readers of the New England Journal of Medicine. As you can see from the enclosed copy, the manuscript was originally sent to Science. I have talked with Dr. DuShane who agrees the article is more suitable for a medical journal. If you agree this work should be reported in the Journal, I will be glad to help with any editorial changes required and serve as the contact point in the United States for Dr. Gajdusek.

Dr. Gajdusek is a brilliant clinical research man who, with support from the National Foundation of Infantile Paralysis, has spent the past two years with Sir MacFarlane Burnet in Australia. On his way back to the States he planned to obtain a few blood samples in New Guinea for work on viruses upon his return. When he learned of KURU there he became so interested in the disease he decided to stay and attempt to learn more of the disease and help those suffering with the condition. When funds ran out the Director of the NFIP made available additional support from the Director's reserve in order that Dr. Gajdusek might continue investigation of KURU. The National Institutes of Health have also been helping with the studies by providing certain equipment and by performing neuropathology and other studies on materials received from Dr. Gajdusek.

I hope the New England Journal of Medicine will publish a report of this disease. Please let me know if I can be of help in expediting the publication of this work.

Sincerely,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. Joseph Garland
Editor, New England Journal
Of Medicine
8 Fenway Street
Boston 15, Massachusetts

cc: Dr. DuShane

CGBAKER:jmh

KURU RESEARCH
OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
17 June 1957

Editor-in-Chief
SCIENCE
Journal of the American Association
for the Advancement of Science
WASHINGTON, D.C. - U.S.A.

Dear Sir:

Enclosed you will find a manuscript by Dr. V. Zigas and myself submitted for publication in SCIENCE entitled:

KURU....A Localized "Epidemic" of Chronic Progressive
Degenerative Disease of the Central Nervous System in
Children, Adolescent and Adult Natives of the Eastern
Highlands of Australian New Guinea

I am an American pediatrician and virologist from Harvard University, a Fellow of the National Foundation for Infantile Paralysis who has completed 2 years of work on a Foundation grant with Sir MacFarlane Burnet at the Walter and Eliza Hall Institute in Melbourne, Australia. On my return to the U.S. via the Australian Trust Territories I have encountered a most astounding illness in Highland natives which has been the cause of our institution of an intensive study of the disease in this remote part of the world. Through the helpful cooperation of Dr. Joseph E. Smadel, Associate Director of the U.S. National Institutes of Health in Bethesda, Maryland and Dr. Thomas Rivers, Director of the National Foundation for Infantile Paralysis, I have obtained a further grant to continue this most interesting investigation.

The scope of our work is ever broadening and the implications ever widening. Thus, it is now evident that the definitive preparation of our data for publication will be greatly delayed--for at least many months, perhaps a year--and that a large series of highly technical papers will be presented in the medical literature. In view of this, my collaborator and I are submitting this first report of this most astounding new illness to your journal in the hope that it may be published at the earliest possible date and gain thereby the attention of geneticists, biologists, ecologists, chemists, toxicologists, nutritionists and anthropologists in addition to the medical audience which will read our later publications, for the problem of KURU is a wide one which should interest many allied basic scientists. Furthermore, it demands immediate attention from those diverse disciplines who are qualified to contribute to its

investigation. Will you please inform me of the receipt of this manuscript and later of any editorial comments by AIR MAIL, for surface mail may be delayed many months in reaching us here among the Forei?

Sincerely yours,

/s/ D. Carleton Gajdusek, M.D.

D. Carleton Gajdusek, M.D.

[SCIENCE Publications]
1 July 1957

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda 14, Maryland

Dear Dr. Smadel:

Would you please advise us about the enclosed paper by D.C. Gajdusek and V. Zigas on "Kuru...A Localized 'Epidemic' of Chronic Progressive Degenerative..." which has been submitted to Science?

It is possible that Science might be a suitable place for the announcement of a new disease of this kind, but I should appreciate your advice on this point. I should also like to know whether the work seems to you to be sound and whether the National Institutes of Health is giving financial support to this work.

If the paper should seem to you to be suitable for Science, I would appreciate your suggestions about how it might be shortened to a length of a report (1200 words, including tables and figures.) In its present form it is very loosely written and rambling and quite unsuitable for publication as either a report or an article.

Sincerely,

Graham DuShane
Editor

Enclosures

[SCIENCE Publications]
3 July 1957

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda 14, Maryland

Dear Dr. Smadel:

Dr. Baker yesterday afternoon suggested that you would be glad to transmit the article by D. C. Gajdusek and V. Zigas on "Kuru...A Localized 'Epidemic' of Chronic Progressive Degenerative..." directly to the New England Journal of Medicine which might be an appropriate outlet for it. It is my understanding that you have been in close enough touch with Dr. Gajdusek so that this procedure would offer no difficulties.

For your information, I am enclosing a copy of the letter of transmittal. Thank you for your cooperation.

Sincerely,

Graham DuShane
Editor

Enclosure

KURU. A LOCALIZED "EPIDEMIC" OF CHRONIC PROGRESSIVE DEGENERATIVE
DISEASE OF THE CENTRAL NERVOUS SYSTEM IN CHILD, ADOLESCENT AND
ADULT NATIVES OF THE EASTERN HIGHLANDS OF AUSTRALIAN
NEW GUINEA

D.C. Gajdusek¹ and V. Zigas²

¹ Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

² District Medical Officer, Public Health Department, Port Moresby, Territory of Papua and New Guinea.

During the past two years' service as Medical Officer of the Kainantu Sub-District, Eastern Highlands of the Australian Trust Territory of New Guinea, one of us (V. Zigas) has had the opportunity of observing in the inhabitants of the mountain-dissected highlands some 30-50 miles southeast of Kainantu an unusually high incidence of a Parkinsonism-like syndrome affecting children and adults, predominantly females, in natives of the recently controlled Fore Linguistic and Cultural Group and in their neighbors of the Keiagana, Kimi, Usurufa, and Auiyana Linguistic Groups. During the past three months an intensive clinico-pathological and epidemiological study of the strange "epidemic" has been conducted by us with the support and assistance of the Department of Public Health of the Australian Trust Territory of New Guinea, and this study is continuing. The current report of our preliminary findings is based on the careful study of 78 cases of this new disease which the local populace know by the name of KURU, a word which also has the meaning "to shiver" in Fore. These clinical observations along with further epidemiological study suggest a possible genetic etiology or, at least, hereditary predisposition for this unusual condition. Thus, it seems most closely related to the ill-defined group of heredofamilial neurological degenerative disorders of the central nervous system, particularly to the cerebellar and spinal ataxias such as hereditary spinal and cerebellar ataxia (Friedreich's ataxia), hereditary cerebellar ataxia with spasticity (Marie's ataxia), olivocerebellar and olivopontocerebellar atrophy, and parenchymatous cerebellar degeneration, and to those heredodegenerative disorders of the basal ganglions which include paralysis agitans (Parkinsonism), hepatolenticular degeneration (Wilson's disease), and Huntington's chorea.

The illness runs an afebrile course and is characterized by the insidious onset of ataxia which becomes progressively more severe and is soon accompanied by a fine tremor involving the trunk, head, and extremities. Both involuntary tremor and ataxia increase, the tremors assuming a typical Parkinsonism-like character with exaggeration during voluntary motor activity or fatigue, subsidence during rest, and disappearance during sleep. There is no evidence of pyramidal tract damage. The reflex pattern usually remains normal with no extensor plantar response or sustained ankle clonus, although occasional patients demonstrate a symmetrical hyperactivity of tendon jerks, while others show hypoactive responses. No sensory changes appear, nystagmus is not present, there is no greenish-yellow pigmentation at the scleral-corneal border (Kaiser-Fleischer rings), and the optic fundi remain normal. No evidence of systemic disease, particularly of liver involvement, can be found.

Involuntary tremors, ataxia and incoordination continue to increase in severity for one to three months from their onset--an occasional case runs a more slowly progressive course--by which time the patient usually requires the support of a stick for walking. A month or two later the patient is no longer able to walk or stand at all without extensive support and equilibrium in the sitting posture is soon thereafter impaired. Intelligence remains normal during the early months of illness, but speech slowly becomes blurred and slurred and finally no longer intelligible. Together with this dysarthria a progressive slowing of intellectual function is apparent.

The patients often display a marked emotionalism with excessive hilarity, uproarious, foolish laughter on slight provocation, and slow relaxation of emotional facial expressions. Occasionally withdrawn, sullen behavior appears, accompanied by the mask-like facies characteristic of Parkinsonism. A few patients become belligerent and aggressive. These are often passing aspects of behavior and, in general, the patient remains well integrated in his social setting until he slowly falls into greater and greater incapacitation. When the patient is no longer ambulatory in the native setting he is usually left to die in the low, dark kunai grass habitations and seldom if ever is carried out into the sunlight. Urinary and fecal incontinence develop and speech is completely lost, although there may remain evidence of comprehension from eye movements, occasional voluntary motor responses and grunts. Finally, swallowing and chewing are no longer possible and the helpless patient succumbs to rapid starvation, decubitus ulcerations and terminal static bronchopneumonia. In the late stages of the disease a flexed posture, already evident earlier in the illness, is most usual, but muscular contractures are very late in developing. Muscular spasm--occasionally a cogwheel type rigidity--usually develops late in the illness and repetitive, periodic choreiform and athetoid movements may appear, especially when the patient is disturbed. There are no muscle weaknesses or paralyses and no muscular atrophy early in the illness. No generalized convulsions occur. A convergent strabismus is a nearly universal late development in the disease.

Kuru rarely lasts much over one year, and is often fatal within three to six months of the onset in the village setting. Remissions or recovery are very rare. In our series of 78 studied cases, only one has remitted. This, like all those few histories of recovery which we have elicited from the Fore natives, was in a young adult female of decidedly hysterical temperament. It is our current hypothesis that an occasional case of hysterical mimicry of the early ataxia, incoordination and rather violent tremors of Kuru occurs and that this accounts for those few remissions or recoveries which occur. No advanced case of the disease has recovered, to our knowledge. These rare recoveries from Kuru, traditionally a sorcery-induced malady, are attributed by the natives to counter-magic.

Kuru occurs after four to five years of age and predominantly in females. Our youngest patient is a boy of four years. In the prepubertal ages over two-thirds of the patients are girls. In adolescence, when the incidence is apparently somewhat lower than in the prepubertal years, the female:male ratio is more nearly 1:1. Among adults, in whom some 65% of the cases occur, the female:male ratio is over 15:1.

Laboratory studies have not yet revealed any regular or striking abnormality. Thus, examination of cerebrospinal fluid on 55 of our cases has revealed no pleocytosis or increase in globulin (Pandy reaction) or total protein, and CSF sugar and chloride levels and colloidal gold reactions have, in general, been normal. Enumeration of erythrocytes and leucocytes and hemoglobin determinations have been unremarkable as have urine analyses. Liver function tests on several patients have been normal as have blood urea nitrogen determinations. Sedimentation rates have been highly variable: low in the majority of patients but greatly elevated in others, and intercurrent infections have not always been demonstrable to account for such elevations.

Serum protein estimations (total serum protein, serum albumin, total serum globulin, and serum gamma globulin levels) have revealed unusual globulin patterns which are, however, characteristic of many sera from New Guinea Highland natives not suffering from Kuru. Paper electrophoresis studies of sera and of hemoglobins from our patients have been performed by Dr. C. Curtain of the Baker Institute in Melbourne. Enormous elevations of beta globulins in many cases, and high alpha globulin levels in some have been encountered. These findings must be correlated with results on normal Fore natives, and this matter is being further investigated. No abnormal hemoglobins were found in paper electrophoresis of specimens from a number of Kuru patients.

Blood group testing on 26 Kuru patients for A-B-O, MN, S. Rh, C^w, P, Le^a, Fy^a, and K systems by R.T. Simmons of the Commonwealth Serum Laboratories in Melbourne has revealed a pattern following that reported for Natives of Chimbu, Nondugl, and Mount Hagen in the Central Highlands of New Guinea (1,2,3). Serum titers for anti-A and anti-B were all normal and search for atypical blood group serum antibodies revealed none.

Serum and total blood copper levels on our patients, along with estimation of other trace metals in blood, urine, cerebrospinal fluid, and in tissues obtained at autopsy, were determined in collaboration with Dr. A.V.G. Price of the Public Health Laboratory and Mr. Baseden and Mr. Southern, chemists at the Laboratory of the Department of Agriculture in Port Moresby, Papua. No abnormalities have been discovered. In particular, blood copper levels on a number of patients have been normal or slightly elevated, but no more so than such levels on control Fore subjects.

Six patients have now died under our observation and another six are near terminal. Of the six deaths, autopsies have been obtained on three cases. In two cases, full examination of all organs was possible while in the third, removal of the brain only. No gross pathological lesions were found, notably, none in the brain, meninges or liver. Histological and neurohistological findings will be reported in a further communication. Attempts at virus isolation by Dr. S.G. Anderson of the Walter and Eliza Hall Institute from brain in buffered glycerine and from blood and cerebrospinal fluid sent refrigerated by air to Melbourne, Australia have been unsuccessful.

Extensive clinical trials of numerous therapeutic agents have been conducted and others are under way. The illness has been unchanged and its progress has been uninfluenced by prolonged courses of high doses of acetyl salicylic acid, sulfadimidine, antibiotics (penicillin, chloramphenicol, aureomycin), cortisone acetate, delta-1-hydrocortisone, testosterone, anti-histamines (pyribenzamine or Benadryl), phenobarbital, dilantin, tridione, ascorbic acid, vitamin B complex, folic acid, crude liver extract and intensive courses of BAL therapy such as those which have been reported as effective in hepatolenticular degeneration.

Thus far, we have been unable to elicit any consistent history of mild or severe antecedent illness which might be interpreted as an acute infectious

disease. We have been unable to note any seasonal variation in time of onset among our Kuru cases. There is no tradition nor memory of any epidemic or encephalitic illness among the Fore. In our three months of Kuru investigation we have been operating a regional hospital servicing the 30,000 population administered from the Okapa Patrol Post, where our research center and Kuru hospital are located. We have seen during this period epidemic upper respiratory infection and epidemic bronchopneumonia of infants and young children, both of undetermined etiology, and epidemic pertussis, and have encountered cases of acute bacterial meningitis (with identification of the *N meningitidis* in three, *D. pneumoniae* in one, and *H. influenzae* in two) in native children. We have not seen any case of encephalitis or benign aseptic (lymphocytic) meningoencephalitis, although CSF examinations have been literally performed on any suspected infant, child or adult. Thus, no illness which we have observed could be interpreted as an acute infectious disease regularly antecedent to or occurring at the onset of Kuru. New cases of Kuru have developed during our three month period of intensive investigation. Few of our cases admit to any acute antecedent illness, although headache accompanying the onset of illness is described by some one-third of the patients. When a history of such acute illness antecedent to the ataxia is obtained, it is never described as incapacitating or interfering with ambulation and other normal activities of the patient, and headache, knee pains, cough, coryza and fever are the only prodromal symptoms--in order of decreasing frequency--which we have elicited in anamnesis, but these we have not yet observed. Kuru is apparently not of post-infectious etiology.

Kuru occurs only in a small region south and east of Mount Michael (elev. 12,500 ft.) in the mountainous southern portion of the Eastern Highlands of Australian New Guinea. This is an area of rough terrain and kunai grass-covered or heavily forested slopes, mostly lying between 5000 and 7000 feet above sea level. The majority of the affected population lives at elevations at which malaria is not encountered in these highlands. Kuru has not been seen in Goroka, Kainantu, Wau, Bulola, Lae, Mount Hagen or Madang, the nearest government stations where medical treatment and observation of natives has been in progress for over twenty years, nor anywhere else in New Guinea or Papua. Sporadic cases of Parkinsonism, or paralysis agitans, have been observed at Chimbu, Mount Hagen, Lufa and Goroka in highland indigenes, but no case of rapidly progressive and fatal disease with ataxia and tremors which might be interpreted as Kuru. Among the Fore we have encountered one case of severe congenital tremor in an adult male over thirty years of age whose tremor dated from infancy or early childhood and was unassociated with other features of Kuru. The illness is restricted to natives of the Forei Linguistic and Cultural Group and to their immediate neighbors. It has been found in every village inhabited by Fore people, but it occurs only in those portions of the region inhabited by Keiagana, Kimi, Auiyana and Usurufa peoples which are immediately adjacent to the Fore and in which intermarriage with the Fore has occurred long before Caucasian contact. Portions of these other linguistic groups more remote from the Fore have not experienced the illness. The total population of the region in which Kuru occurs is about 15,000 of which the Fore comprise some 10,000. In this region we have located and have regularly examined 78 patients with active progressing Kuru. It is estimated that at least an equal number of cases remain in little-accessible hamlets which we have not yet visited. Exhaustive enquiry has already yielded a history of some 300 deaths from Kuru in the past five years which have been

verified by careful cross-checking of information, and this documentation has not yet covered more than one-half of the population in the Kuru region. About one percent of the affected population are currently afflicted with Kuru, and at least one percent of the population has died yearly therefrom in recent years. Since the illness rarely has a duration of over one year, this situation is apparently continuing at present. In certain Fore Clans and Tribes the current incidence of active Kuru reaches five to ten percent of the population, and over 50% of all deaths in some of these communities over the past five years have been from Kuru. Interrogation of native informants whose reports are verified by independent cross-checking reveals that Kuru has been present for at least twenty years. A few well-verified cases occurred twenty to twenty-five years ago. Government control of this region has existed for five years or less, and prior to that cannibalism, interclan warfare and ritual killings--remnants of all of which still survive--were prominent features of Fore culture. The first European contact which the Fore peoples experienced was that of Ted Eubanks, who discovered the Okapa pine forests in Fore territory in 1932, while prospecting for gold. Until the current decade very little attempt to establish government control was exerted. Thus, Kuru cannot be associated with the entry into the region of Europeans. However, intertribal trade routes may have introduced certain new crops and occasional manufactured items before European entry. Aside from the Europeans whom our investigation of Kuru has brought into this region, the total European population in this region of 30,000 native population is two: a Lutheran missionary and the government patrol officer at the Okapa Patrol Post. Early contact patrols some five years ago already noted this "shaking disease" in their reports. Old informants usually add that the illness was not present in their youth, but there is no way of assessing the reliability of such affirmation.

Thus far, no natural geological or ecological discontinuity can be associated with the boundary delimiting the Kuru region. All the Fore people are affected, and in the narrow belts of Kuru occurrence in the Keiagana, Kimi, Auiyana and Usurufa tribal grounds the only ethnological discontinuity which can be associated with Kuru is that between members of these other linguistic groups who have frequent intercourse with Fore peoples, and those who do not.

As in any native society, a complex kinship system exists among the Fore (6), but reliable enumeration of the pregnancies of any child-bearing woman can be readily obtained. Such information reveals a family history of Kuru in one or more close relatives in over half of our cases and in parents or siblings in 43% of our 78 currently studied cases. Since villages and hamlets range in population from a few dozen to several hundred inhabitants and close intermarriage is therefore the rule, it would be difficult to find a "control" family without a similar history of Kuru, for any extended family tree is likely to have a current case or recent Kuru death.

The etiology of Kuru, therefore, remains obscure, and no aspect of nutrition or other feature of Fore culture has yet revealed any clue as to what environmental factors are operating in its pathogenesis. The peculiar sex and age distribution of cases, the high familial incidence in a closely intermarried community, the phenomenon of anticipation (with cases occurring at an

earlier age in the second generation), and occasional family histories wherein several siblings have died of the disease on reaching approximately the same ages, along with the type of clinical picture the disease presents, all support the suspicion that strong genetic factors are operating in the pathogenesis, probably in association with as yet undetected ethnic-environmental variables.

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6. Berndt, R.M.
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[NIH]
July 5, 1957

Dear Dr. DuShane:

As mentioned in our telephone conversation on July 3, Dr. Smadel is submitting the manuscript by Drs. Gajdusek and Zigas to the New England Journal of Medicine. Some revision of the manuscript has been made in an effort to improve the presentation. A copy of the correspondence to the New England Journal of Medicine is enclosed for your information, and Dr. Gajdusek has been informed of the action.

Sincerely yours,

Carl G. Baker, M.D.
Assistant to the Associate
Director

Dr. Graham DuShane
The American Association for the Advancement
of Science
1515 Massachusetts Avenue, N.W.
Washington 5, D.C.

Enclosure

[NIH]
July 2, 1957

Dr. D. C. Gajdusek
Pintogori, Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea

Dear Dr. Gajdusek:

I have been asked by Dr. Joseph Smadel to provide various logistical services for you. Arrangements have been made to analyze the blood and urine samples you have shipped to Dr. Smadel, and one of our investigators is conducting neuropathological studies of the tissue specimens you collected.

The six rolls of film you sent have been developed, and color prints are now being made.

We are sending you a 16 mm. motion picture camera (Bolex H-16) with case, heavy duty tripod, exposure meter, and polyethylene bags and silica gel to help you in protecting the equipment from dampness. We are including eight 100 ft. 16 mm. rolls of color film, four 100 ft. 16 mm. rolls of black and white film. Thirty-six one-dozen packages of Keidel-type vacuum-tainers (bleeding venules), which will make possible your collecting and preserving blood specimens which will remain chemically and bacteriologically sterile, will be forwarded shortly. Experts in photography and investigators who have conducted field studies under conditions such as you have described were consulted in the selection of the photographic equipment and bleeding venules.

As a matter of record, please sign (beside red check) and return the enclosed property loan forms; this formality is required by the regulations of the Public Health Service and the National Institutes of Health.

When you are finished with the equipment would you please send it to me; transportation charges will be paid by us.

Sincerely yours,

Eckart Wipf
Administrative Officer
National Institute of Neurological
Diseases and Blindness

[Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of New Guinea]
8 July 1957

Dear Joe:

Enclosed is a copy of a recent letter to Dr. Abbott, currently Acting Director of Health, letting him in on our work. It should serve to inform you of what we are up to also.

I have some two or three letters out to you at the moment, and am anxiously awaiting even a few words of comment on the brains we have sent and the manuscript. From current notes from Melbourne, they are now down to 4% formaldehyde (i.e. one part 40% formaldehyde--i.e. Formalin--in nine parts of saline) for fixation, whereas we have used either 10% or 15% formaldehyde for the four brains we have already obtained, three of which are off to you. Furthermore, Melbourne--only Graham Robertson is looking at the brain, and he has had only one thus far, our first--requests a thorough perfusion of the brain before fixation. This procedure I shall try, but we have no appropriate canulas, nor is the cold wind and rushed excitement of "bush autopsies" conducive to careful and accurate perfusion. We shall, however, do what we can. I would very much like added word on:

- 1) value or lack of value of perfusion, and any suggestions for doing it well in the bush...we have a good roof, syringes and needles, and might even get i-v saline through, if we had canulas to tie in;
- 2) best possible fixation methods. We used 15% formaldehyde on brain which you got and transferred them to 10% thereafter (one to two days later) and sent them once somewhat hardened; and
- 3) any detailed suggestions for more elegant preparation of brains and other path specimens--since first report from Melbourne claims nothing much on neuropathological study, other than ?diminished cells in cerebellum.

Our patients are dying of advanced neurological disease, and many with death imminent are on our hands, and brains and full autopsies may be possible. Thus, we might be able to supply whatever your neurohistologists and general pathologists desire, if you only tell us. Cases now total over 110 and we have some thirteen deaths since we started studying, and I suspect all the others will go the same way within one to two months.

Enclosed is a copy of most of our record on Yabaiotu, a woman whose brain was shipped off to you last week. Histories on the other two specimens are already in your hands, I believe, as well as that on Kinao, our first autopsy, viscera on which you received...the brain went off to Melbourne. Your records should thus be complete. Please ask those who

look at the material to keep in touch with us, for here in the bush any and every lead may influence the course and direction of our work.

The markedly abnormal beta-globulins found in many of our sera need further study. Lois Larkin is going to mail the entire extensive kuru serum file off to you as soon as she returns to Melbourne. Thus, you will have all the serial specimens on the patients, as well as many control sera for eventual serological study or--perhaps more important--further check on the protein abnormalities Cyril Curtain has been finding on the specimens he got from us in Melbourne.

I have written to Tom Rivers and thanked him for his great assistance. If you think that the current letter contains anything he should see, let him see it. There is not much new since my last long letter to you and to him, just plenty of work. Tridione, testosterone and second courses of BAL are the current therapeutic regimens being tried. We never did get any of the anti-Parkinsonism drugs into our hands I hear about from the U.S., and if you can track us down a supply of them with literature, I should be most interested.

Sir Mac has a paper follow-up on my AICF paper, and many are jumping on the bandwagon. That it is a really hot test in certain macroglobulinemias and most DLE's, is certain and I beg you to ask anyone who might have multiple myelomas, macroglobulinemias, disseminated lupus cases, and this type of case on his hands, to save (at -20°C) serial serum specimens for me. I shall rush through them immediately upon my return. The Melbourne crowd has kept actively up with my test, and it is proving most intriguing in certain cases of DLE and other diseases. The two definitive papers still held up by Archives of Internal Medicine have me angry...there will be a whole series of "follow-up" papers by others out before they get off their editorial asses, unless they hurry up. I hope they write soon.

Sincerely,

/s/ Carleton

Carleton

33a enclosure

Okapa Patrol Post
via Kainantu, E.H.
Territory of New Guinea
July 4, 1957

Dr. T.K. Abbott
Director of Public Health
Department of Health
Port Moresby
Territory of Papua and New Guinea

Dear Dr. Abbott:

I thank you for your kind letter of June 4th and I beg that you excuse my laxity in keeping you informed about Kuru Research. I have been so rushed that reports have simply not been forthcoming. We have had a total of twelve kuru deaths among the 110 kuru patients we have now brought our total "Active Kuru Cases" to, and of these we have had four autopsies--three complete and one with brain only obtained. We are awaiting reports on histopathology, but thus far preliminary communications inform us of nothing startling, except, perhaps, a slight diminution in cells in the cerebellum. Grossly, we found nothing remarkable, and thus Wilson's hepatolenticular degeneration is fully ruled out.

I had arranged for thorough blood group genetics to be done on kuru patients' red cells and serum (including abnormal hematological antibody studies) and these have been completed on some 44 by Roy Simmons, with whom I have collaborated in the past. These results may eventually be of value when it is possible to compare them with normal non-kuru control groups and with Fore, Keiagana, Kimi studies, specimens for all of which studies we have already been collecting. If things do work out to substantiate the current suspicion of a strong genetic predisposition as perhaps important, if not determinant, in this disease, then such studies will be of immense value. They are already partially completed.

Other collaborators have managed to detect rather startling protein abnormalities in some of our patients, and we are pursuing this matter at length. Of course, it again must be controlled by normal Fore and other Eastern Highlands populace studies, which we are trying to carry out. Dr. A.V.G. Price has been of immense help to us and we are sending him many specimens--blood, urine and autopsy--for trace metal studies and other clinical investigations. He has supplied us with everything we have requested, made valuable suggestions, and provided many important determinations. Thus far, we have no evidence of copper toxicity from the data he has sent us, but many other trace metal studies are under way.

Antibiotics, sulfonamides, phenobarbital, acetylsalicylic acid, dilantin and tridione, cortisone, delta-hydro-cortisone, testosterone, and B.A.L. have all been tried without any dramatic effects. We are still trying B.A.L. before we can be certain that it is ineffective, and since a single course requires three or four injections on day 1, and twice

daily injections for four to five succeeding days, the supply of ten packages (12 ampules of 2.0 ml each) which S.G. Anderson brought up, on my request, was soon exhausted and the new supply of three boxes is only enough to give a second course--which is now due--to four of our patients, children, at that. Could we get a further supply of B.A.L. (oily injection of Dimercaprol)? We have ample Tridione to complete the current clinical trial on eleven well chosen cases. We did not have ample Dilantin Sodium, however, to make the trial of it a fully satisfactory clinical investigation, and if more could be supplied, we should be most grateful.

Testosterone and stilbestrol investigations are only now starting. We will need a further supply of testosterone propionate or methyl testosterone for this work, if it can be provided. The marked sex inequality in the distribution of our cases provides the basis of therapeutic trials in this direction.

I have just recently returned from 18 days of patrolling in the Baro Ianai (Yani River) Basin area, where I located Kuru far south to the most southerly extent of the Fore, in high incidence (4% of the most southerly Fore community were currently suffering with active Kuru). However, what was more important, I found the limits of kuru for fully half the circumference of the kuru-affected region, and in this region of kuru--non-kuru boundary, epidemiological study proves much more profitable and rewarding. Here it is possible to find isolated kuru cases in almost kuru-free communities, and to contrast lineages and households with kuru with those without kuru....and to compare kuru-present with kuru-free communities of the same cultural stock. Such studies are not possible in our Kuru Research Center at Moke-Okapa, for kuru incidence is so high that there are no "control" households or lineages or hamlets.

In the low-kuru incidence region I could trace many cases to Fore women brought into the community by marriage. Some were from Fore families with much kuru in parents, siblings and other close relatives, and the Fore girl, married into the Kimi, developed kuru in the virtually kuru-free Kimi community only after years of residence there. This would seem to cinch the genetic matter, were it not for a few--decidedly in the minority--cases still to be further investigated of Kimi girls from low-kuru incidence communities developing kuru when marrying into the Fore kuru region. Thus, matters are by no means clear as yet. However, it is essential to delineate the kuru boundary, for it is here that investigations may prove most valuable and study of this boundary and any shifts in it may, in future years, provide valuable data on kuru and its behavior. I certainly hope that before then we may locate some other factors of importance in pathogenesis or some specific etiological agent for kuru, but thus far we are faced with no leads which have led to anything but a further incrimination of the discouraging genetic-familial hypothesis.

Lucy Hamilton is with us, giving us a fine hand in tracking down dietary practices. Toxic factors keep suggesting themselves, but none has yet proved a very tenable possibility. It will require something mighty unusual to account for the peculiar 15:1 female to male sex ratio among adult patients, and 3 or 4 to 1 among child patients. The child and early adolescent cases (on whom our studies are concentrated, because of my preference for working with children, and better familiarity in clinical investigation in pediatrics than in adult medicine) comprise some 20 to 25% of the total number of active cases in the region. In general, there are four adult cases to every child or early adolescent case.

We are anxiously awaiting the film unit, but, unfortunately, it was unable to arrive when we had--as we have just had--maximum in-patient census. We are now forced to yield to our patients' insistent pleas and release many of them to their villages. While the film unit is here, we shall do our best to round them up again. We are also planning a patrol to visit a few patients in the fully-native setting. Most of those nearby can no longer be so classified, for we have dressed and bandaged ulcerations, urged supportive measures and, in general, interfered with the native practice of neglect and avoidance once the disease has reached incapacitating stages--practices which, in the long run, may be the most humane, for they ensure a rapid exodus once incapacitation is such that there is no further possibility of entering into any part of normal native social life. Asomeia, one of the two patients we sent to Port Moresby, is now in terminal condition, in very pitiful condition. She cannot live much longer. Manto, the second patient who visited Moresby, is likewise deteriorating rapidly, but is not yet quite terminal.

Our new kuru ward provides ample space for hospital cases and we have finally provided ourselves with good laboratory and treatment room facilities, thus, hospital housing is fine. The new native-materials house for our kuru research personnel--all of whom are still living parasitically on the Kiap, Patrol Officer Jack Baker, who is giving us wonderful assistance--is nearing completion and will provide ample roofing and table space for the work. Funds for patrolling and odd kuru research expenses, Vin Zigas tells me, are fully exhausted, and if there is any possibility of an added grant to cover the costs of trade items, supplies, etc. which are essential if we are to keep finding cases and studying them and caring for them, it would be most welcome.

Please excuse our cable requests for a typewriter. We are using one which does not belong to PHD and which we have borrowed and must return. Furthermore, manila folders, filing cards (several thousand) and a cabinet or boxes to contain them, are essential if we are to preserve the extensive epidemiological records from chaos. The latest cable from Moresby tells us that these supplies are coming, and we are therefore most grateful. As for the typewriter, we shall try the D.C. at Lae, as suggested.

In my latest letter from Bob Traub, Commanding Officer of U.S. Army Medical Unit at the Institute for Medical Research, Kuala Lumpur, Malaya, Bob mentions how very helpful you were to him in Borneo and urges me to look you up. From all Vin Zigas has told me of your interest in kuru, and from all the Traubs have told me of your interest in investigative work, I am certainly most pleased to have this opportunity to correspond with you, and when kuru research is more settled, I shall certainly hope to meet and discuss matters with you and Dr. Gunther in Moresby. At the moment, I am trying to complete as accurate and thorough an epidemiology as possible, for should we be stale-mated by kuru, as we shall be if all the suggestions that it is a degenerative heredofamilial disorder of the CNS, rather than a toxic or post-infectious phenomenon--no evidence for which we can yet find--then, the most important contribution we can make to kuru study and to the field of human genetics is a thorough incidence, distribution and case density pattern survey as a baseline for follow-up studies in future years. It will then be the future behavior of kuru in this and surrounding communities which will give us the added precious information. At the moment, however, without a fully validated epidemiological record of the illness, future patterns could never be interpreted, for there is nothing to refer them back to. Thus, our rather ambitious current goal is to document every kuru death in the memory of the 15,000 affected populace, check these by cross-interrogation and the extensive family histories of our current cases, and to plot this data out on a population map and tribal-linguistic map of the region, which we are now also compiling with the extensive aid of P.O. Baker, who has given much of his administrative time to helping us on our kuru study. This ambitious project is over half-completed already. When the kuru perimeter is fully substantiated and patrolled--and this too is over half-finished--the current phase of kuru study will be over. By that time we should have simultaneously completed adequate therapeutic trials of all medications which we thought offered some promise, and also have carried out as thorough a clinical study as bush conditions will permit. At that phase I shall try to travel to Moresby to see you and others interested in kuru, and I hope that Vin Zigas, on whose shoulders so much of the work and support in this study lies, can accompany me.

I hope you will not mind my boldness in summarizing herewith the supplies and drugs which we see no chance of getting through usual channels of order and supply:

- 1) B.A.L. (oily injection of Dimercaprol), 10 to 20 boxes of twelve 2.0 ml ampoules each.
- 2) Testosterone propionate, either as methyl testosterone or as the propionate.
- 3) Any of the modern tranquilizers, none of which we have been able to get our hands on for a trial in severe kuru.
- 4) Dilantin - sodium, enough for a trial of one to two weeks' full dosage medication on some ten patients.

We are pleased to learn that Kako, the Fore girl with patent ductus arteriosus, whom we found in our studies and sent to Moresby for ligation,

has been operated upon successfully. Our error in sending the full case history, not with the patient, but in our report letter on kuru to Dr. Scragg, may have caused some unfortunate delay in the appropriate people getting her case history...we are sorry. Thus far, we have not seen the patient again, but hope she will soon be back in her village, where her kinsmen are inquiring about her.

Finally, Dr. Abbott, please excuse my addressing you improperly, if you are not now Acting Director of Health. I do not know whether you or Dr. Scragg has the post, at present, and I have wanted to thank you for your letters and assistance. Will you please show our report of current work to Dr. Scragg and Dr. Gunther, both of whom have asked to be kept informed of its progress.

Sincerely yours,

/s/ Carleton

D. Carleton Gajdusek, M.D.

/s/ V. Zigas

V. Zigas, M.D.

[Okapa Patrol Post
Kuru Research]
10 July 1957

Dear Joe:

Only two days after writing the enclosed letter, and still no way to get mail out to Kainantu, and our cases have jumped to over 120 active cases in our Study Series and we have had two further deaths with complete autopsies. Both were complete autopsies, done immediately after death and brain obtained less than one hour post mortem. Thus, we have two further brains on our hands already--one for you and one for Melbourne--and both went immediately into 4% formaldehyde and will be changed daily to fresh formaldehyde until hardened.

Please rush details of more elegant fixation or, at least, straighten out the conflicting percentages and directions.

Enclosed is also a long manuscript of our second kuru report, the first off to an Australian journal, which we must do for political reasons. It was only written yesterday, but is already out of date, for I have now brought our study cases to over 120, and we have these two further autopsies.

In addition, we have just received our first early case of acute meningoencephalitis, nothing like what any of our kuru patients have ever had, as far as we can ascertain, but we have a boy of six with 248 cells, almost all mononuclear, in the CSF and mighty sick. We are sending feces, throat washings, CSF and blood off to Anderson in Melbourne today, and hope that the two days' delay in getting there may still net us something. We have nothing here in which to inoculate, other than ourselves, and we have not reached that stage of desperation as yet.

In spite of the interest in this case--our one previous case mentioned in the enclosed paper was recovering when first seen, but still has CSF pleocytosis; we cannot link this sort of illness with kuru, as hard as we may try. And we have only two cases of benign aseptic meningitis, undiagnosed, in four months of study--and over 120 cases of kuru!

Please ask your neurologists and neurophysiologists and internists to read over this paper--and the previous one--and send me any comments, suggestions, corrections or disagreements they can. It is difficult writing and working here in bush isolation, and I sadly feel the lack of colleagues and critical discussion. I shall be most grateful and indebted to you for all and every editorial comment you make, and all that you can secure from neurologists at NIH. This applies to the enclosed and to the previous paper. Both are, of course, still confidential outside of the professional audience who may be willing to proofread and criticize for us.

-2-

A Jeep is at last coming in to take out Vin Zigas with mail and specimens, and I must close and mail this off without further proofreading. Please excuse my unedited reflections, as usual.

Sincerely,

/s/ Carleton

Carleton

[OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea]
25 July 1957

Dear Joe:

Enclosed is a letter and a slightly revised manuscript...no essential changes, just a few grammatical corrections, clarifications and figures brought up to date....to the New England Journal of Medicine, which you chose wisely and, from my point of view, very well when Science suggested a more medical journal. I do not know the exact address and thus beg you to rush the letter and revision off to the journal as promptly as possible.

By now you have no doubt received the follow-up paper just going off to the Australian Journal of Medicine (Medical Journal of Australia, to be exact), in order to pacify administration about here. However, we are counting on the N.E.J.M. article appearing first--prepared and submitted two months earlier--and thus I write to let them know we are in full accord with their having the paper and to let them know that a series of papers is soon to follow, and thus urge as prompt attention to our report as possible. We know it is a good first report of a new disease and think it deserves prompt handling.

Venules have arrived and they are fine, although the 6 to 8 ml size often leave the labs screaming for more serum! We are most grateful. We also have extensive new studies under way about which I shall write shortly. Just off to you are two new brains, whole brains, from two typical cases on which we have observed progress from early to terminal disease. Both are from children: Aranaka, a boy of about seven, and Mulinapa, a girl of seven to eight. Both died of typical childhood kuru, rapidly advancing. Also, Zenkers and 5% HCHO fixed tissues on Mulinapa are sent (from a wide range of viscera, muscle, fascia, etc.), and the same range of tissues (but only HCHO-fixed) on Aranaka (in this case in the brain tin, along with the brain).

We need, more than ever, some idea of what, if anything, pathology is showing, since we soon will call an end temporarily to field work and any possible leads may determine the course of our further work these last months. In addition to all this, there are Zenkers-fixed (now in 70% ethanol, as usual) and 5% HCHO-fixed liver, kidney, spleen, on a case of rapid liver coma death with slight ascites in a chronic liver failure case with rather acute symptoms and rapid exodus. This pattern in well-nourished individuals, in a well-nourished community in which we have yet to see clinically diagnosable infectious hepatitis, is not uncommon in both adults and children, and we would like some pathological study, for its etiology may be of much importance to

our work and to medicine here. Liver--as is obvious from the chunk--was shrunken, nodular and firm; spleen slightly enlarged, hyperemic; kidney a bit small.

The enclosed letter from Qantas , with the reply I have just cabled them, will let you know what has happened to the photographic supplies we urgently require and most anxiously await. Since I do not suspect that they were dispatched with a \$250.-odd shipping charge waiting for me on this end, I suspect Qantas is, as usual, in error. Especially since the venules arrived O.K. with the U.S. Government address and information label obscured by various other "Collect" labels which could easily be misinterpreted. However, to make sure Qantas does not take a month or more straightening out the mess while they sit on the camera, etc., could you ask the initial carrier in the U.S. (probably PAA) to cable Qantas, Lae some clearing order, just in case things get really snarled up at Lae--as they are apt to, unless, of course, they have already heard from Qantas by the time you get this.

More study of our patients and the help of some clinical visitors has thrown us more into doubt than ever as to just where the neurological lesion is. Emotional instability is certain, a tendency to excessive hilarity, etc. is certain. The "mask-like" facies is rather a fixed-facies --but not "mask-like"; i.e., it is full of expression, but quiet, with rare blinking and little motion until stimulated. Then it responds quickly and usually somewhat excessively, with euphoric grins and smiles, or even shrieks.

The entire postural tremor situation is most complex. It is not a true cerebellar, nor a true Parkinsonism tremor. It is rather a tremor and other types of involuntary movements which are very irregular and difficult to describe. It is definitely an anti-gravity, postural disorder. Thus, sleeping, or when curled up and firmly supported in any position--i.e. in another person's arms, pressed tightly in another's grasp, etc.--the tremor disappears. Any sudden relaxation of this passive support, or sudden shift of even one portion of the body's posture (as of the head, neck, one arm), produces a violent tremor plus choreiform response in the entire body, aimed, apparently, at reestablishing a difficult to maintain antigravity equilibrium. Toes are constantly gripping and searching when a patient tries to stand unaided, or if more advanced, even when supported. Sudden loss of anti-gravity postural support, given passively by examiner to head or upper extremities, suddenly sets off repetitive, irregular tremors or a choreiform pattern of movement. Rigidity is minimal, if at all present. It appears late. Instead, there is a tone to the muscles associated with attempts at maintaining posture and preventing the anti-gravity tremors which fight the slightest instability of stance, sitting, lying, head posture, etc. and initiate as a startle response. If well and firmly supported passively, even in late cases, this "intermittent rigidity" subsides to complete relaxation. This more detailed description may

help some neurologists further locate the lesion for us. Please tell them to pass on their ideas. Nystagmus is absent; Babinski has not yet been positive; but ankle and patellar clonus are not rare in very advanced cases. When present, patellar clonus and ankle clonus are sustained and definite...only a certain few advanced cases show these.

Joe, please urge the NEJM to get our paper out before the "follow-up" studies start to appear. They have a chance at the "first report" and I think it is one worth taking!! We are referring in the second and third papers to our previous "preliminary" report, which we now hope will be NEJM.

Since the paper is now off to a medical journal, we might as well show a picture or two of the illness at the start. Of the black and white negatives sent to you, a certain group of frames were designated for enlargement for possible publication. If you could select the most informative among the following, look them over, and send two or three to the NEJM, along with copies to me to label and describe and decide definitively on, it might greatly improve the paper. I am referring, of course, to the black and white still negatives we sent to you:

Film 1: Frames 10, 11, 12---all three kuru children have now died.

Frames 34, 35, 36, 37---Aranaka (whose brain is now en route to you).

Frames 20, 21, 22---Kinao, who has died of kuru.

Film 2: Any of these--all show kuru patients--on this roll, which show kuru well, especially any showing strabismus or the laugh.

Although we have many other films, Joe, these two are the only ones now readily available in your hands, and from them you should be able to pick a few shots worthy of illustrating our "first report". If you will send these to the NEJM, and copies to us, we shall be most grateful.

Many new developments are on hand, and I shall shortly try to prepare a new review for you. However, we beg you to push for early publication of our first report in NEJM.

If I can finish our work, the Kukukuku patrol and the epidemiological delineation of kuru in time, I shall try to join you in Bangkok. Can you get

me an invitation to present any of our kuru material? Or should I save it? We will have prepared by then a fairly definitive article for an American journal...it may be of such length as to appear in two to three sections. Furthermore, the pediatric study of our child cases--over two dozen of which we have studied most intensively--will also be prepared later this year.

Chronic manganese toxicity, as described in E.J. Underwood's "Tracer Elements, Human and Animal Nutrition" (1956) has come to our attention, and although not what we are seeing, it can be in Moroccan miners so suggestive of kuru, that we are most intrigued. Yet we cannot find a clue as to the toxin source in our women and children patients. Please tell the NIH neurology group to rush to us any suggestions, further ideas, and advice. We need it, for we are ever being more and more shoved into the genetic corner--the least promising, I fear, but--if so, the most demanding of thorough epidemiological study in these days of radiation and mutation behavior speculation.

I hope you had a fine trip in Europe. Tell me of it.

Sincerely,

/s/ Carleton

Carleton

THE UNIVERSITY OF WESTERN AUSTRALIA
DEPARTMENT OF PSYCHOLOGY
ANTHROPOLOGY

Nedlands, W. A.

July 9th, 1957

Dr. R.F.R. Scragg
A/Director of Public Health
Department of Public Health
Port Moresby, N. G.

Dear Dr. Scragg,

Thank you kindly for your letter of June 21st, 1957 (ref. No. 32/35/M1032 - RS/O'D), in reference to the presence of a disease known as "Kuru" in the Eastern Highlands of New Guinea. I am sorry I was unable to reply to this immediately, but have been inundated with work just lately.

Yes, I am interested in your comments on "Kuru". My wife and I had two periods of field work in that region, within the linguistic blocs of Kamano, Usurufa, Jate and Fore, working first from Kogu and secondly from Moke-Busarasa. During this time we both saw and heard of a number of cases of this, which is known in pidgin English as "guria" (possibly a derivation of chorea?). "Kuru", if we remember rightly--without looking up our notebooks--is both the Fore and the Usurufa word for this condition, known by other local words among the Kamano and Jate (e.g., guzigli or guzili among the Jate). I have commented on the similarity of this to the teti shaking which accompanied manifestations of "cargo" movements in that region (see Oceania, 1952, Vol. XXIII, No. 1, e.g. p. 57): the teti or taborabainu is mentioned also in another paper (Oceania, 1954, Vol. XXIV, No. 3, especially on pp. 207-8, and in No. 4, pp. 272-3). Again, I have discussed this form of "guria" incidentally in a volume I am completing: it was (and I assume still is) regarded as a form of sorcery, and is relatively common throughout the Jate and Fore region, with cases also among the Usurufa. In the cases we observed in the Kogu and Moke-Busarasa districts, the subjects could walk with the aid of sticks or with help from others: there were (e.g.) involuntary twitchings, a feeling of 'abnormal' coldness, dilation of the eyes which appeared glazed and watering, and (especially) lack of control over limbs. Despite muscular difficulty in uttering words, they did not appear to be mentally affected, although we did record material inferring this. The attacks are apparently recurrent, the symptoms becoming intensified. We have recorded a great number of cases in what can be regarded as all stages of development of this form of 'sorcery', which has several locally defined subdivisions. The detailed cases make interesting reading. I tried to interest medical authorities both in New Guinea and in Sydney at the time, but without much response. My impression was that this form of guria was psychosomatic, and differed from St. Vitus' dance. If a detailed medical study were to be made, it would be interesting to dovetail it with the anthropological data. Personally I would be pleased to have a

look at any medical data forthcoming from Dr. Smythe's survey, and would be pleased to comment on any aspect which enters my own sphere of competence.

I would say that one hears more about guria in the Fore linguistic area, and much guria sorcery is said to have come from there, but I would not say it was "centred" in the Moke district: to my knowledge it is fairly well distributed through the Jate and Fore groups, as well as to a lesser extent through the Usurufa and southern Kamano. My rough tentative calculation of Fore-speaking people is 10,000 at the very outside; but of course, as you know, the term 'Fore' is used fairly widely, and actually includes a number of differing language-groups. (For instance, it is used in administrative reports from Goroka to refer to people in the far south of Bena sub-district). I would agree that our own observations would tend to confirm that possibly 1% of the population of the particular area with which I am acquainted were affected by this disease. During the course of our anthropological research work we obtained very detailed genealogical data: again, I would agree that it has been present long before European contact; but from genealogies I would infer that up to 30 years is a very conservative estimate.

I would agree that this disease appears to affect women more than men, and affects those of all ages. Our Fore figures aren't immediately available; but in the Usurufa district of Kogu, e.g., in genealogical material involving a time-depth of approx. 50 years, 268 Kogu males are involved, and of these 2 are said to have died of "guria" sorcery: of 226 Kogu females accounted for, 10 are said to have died of "guria". We have no information on what the possible "cause" may be, beyond that which is regarded as magical or supernatural. A number of examples imply that death took place when maggots appeared on the surface of the body: death, it is said 'always' takes place, and no known cures are mentioned: but there are a couple of cases, though, of recovery from "guria".

Perhaps I should comment here on one particular case. When we returned to Kogu for the second time, my wife found one of the local women whom she knew moderately well (Tu'efa) to be suffering from this--as she had not, apparently, been 6 months before. She accounted for it by sorcery performed on her during a visit to Ke jagana (Jate). Although she was having a severe attack, and could not move about without help from others, this did not prevent her from formulating and conceptualizing her experiences, except that she had considerable physical difficulty in articulating words. My wife went to some trouble to explore this point, since one feature of the advanced stages of the disease is said to be a loss of 'mental' as well as of physical control. About three weeks after our return, Tu'efa appeared to be completely recovered, although both she and others declared that she could expect to have further attacks later on. You may be interested to know, however, that shortly before we left Kogu for Moke-Busarasa several women were warning my wife against going further south, owing to the danger of this type of 'sorcery'. Tu'efa, who was present, added "you saw what they did to me", and proceeded to illustrate very realistically the behaviour of a victim. The movements of her limbs (the way she fell to the

floor, and so on) appeared almost identical with those she had displayed when actually suffering the previous attack. My wife even thought for a moment, in fact, that her actions had 'touched off' another attack; but presently she stood up, quite self-possessed, and repeated her warning "That's what we do, so don't go there..."

We are interested to know that Dr. Smythe is working in that region: we do of course know of Dr. Smythe by repute, but have not met him. We assume he is also carrying out linguistic research: it may interest him to know that we have collected a great deal of linguistic material from the Kamano, Usurufa, Jate and Fore: and my wife has a preliminary paper in Oceania on some translation problems in that region. My wife concentrated on the Usurufa and Kamano languages and I on Jate; and we both attempted a little Fore, but we never became so proficient in this, although we have a fair amount of textual and (written) song material in it.

We hope you will keep in touch, and we shall be pleased to elaborate on any of the above points or answer specific questions.

With all best wishes,

I am,

Yours sincerely,

Ronald M. Berndt

32/35

Dr. V. Zigas
Department of Public Health
Kainantu

For your information. I will endeavour to obtain reprints of the Journals mentioned on page 1 of this document for you.

R.F.R. Scragg
A/Director of Public Health
16/7/57

28th February, 1957

Dr. R.F. Scragg
Director of Public Health
Port Moresby

Sorcery Among the South Fore, with special
reference to Kuru.

The following comments refer to portion of the results of an anthropological survey carried out in three Native areas or districts in the South Fore region of Kainantu Subdistrict, Eastern Highlands. The three areas concerned were WANTO'ABARASA, ATIGINA, and KIMI.

Fore Native Areas

From the point of view of Fore social arrangements, the use of the term "native area" requires some mention. These areas, such as Wanto'-Abarasa, Atigina and Kimi have no reference to Administrative arrangements, but are a matter of local Native organization. The Fore themselves consider their Territory to be divided into named areas, each of which recognizes a somewhat shadowy allegiance to a headman, known in the local language as Kamintawa (which means simply "leader", the same term being used for the leader of a Fore local grouping).

In former times, the main function of area kamintawa was as fighting leaders, and it was through their skill in this role that they achieved their rank. The position of kamintawa was, therefore, a shifting one depending on an individual's maintenance of his ability in fighting and war-leadership. With the coming of European peace, only a few years ago, positions of leadership appear to have become fixed as they were at the time of cessation of fighting, since there was now no means of displacement of elderly kamintawa by younger and more virile war leaders. The Fore do not seem yet to have had time to adapt themselves to new circumstances in this respect or to evolve new means by which indigenous leadership (as distinct from leadership through Government appointment) could achieve recognition. For this reason, where former fighting kamintawa have survived they are still pointed out as the leaders of their various areas, though they are in many cases aged and do not play an active part in community life. In a number of cases, however, prestige remains to them as skilled advisors and arbitrators in community affairs, and to enlist the interest and support of such men can be of considerable assistance to a visiting research worker.

In the case of two of the areas mentioned above, the identity of area kamintawa is clear. The Atigina area recognizes Etagi, of the Wanitavi local grouping, as its kamintawa. Manevu, of the Iasui local grouping, is area kamintawa of Kimi. Both these men are now aged and lead somewhat retired lives, but both still have considerable influence on their people's reaction to visitors. I found them extremely cooperative and helpful.

In the case of the Wanto'Abarasa area, the position is not clear, two men now being indicated as area kamintawa. They are Suguia, of the Kamata local grouping, and Nasumbi, of the Anumpa local grouping. Seguia himself said that Wanto'Abarasa has two kamintawa. I did not meet Nasumbi, and was not in Anumpa, so I do not know the reaction of the locality on this point.

Just as area kamintawa had their main function in the field of warfare, so the areas themselves had little other function than that of fighting alliances or units. In ordinary day-by-day political, economic and other social matters, concentration was, and is, on local groupings within the areas. Even as fighting units, the areas do not appear to have been well integrated, and local groupings within an area occasionally fought against one another.

However, from the observer's point of view, distinctions between the Native areas have some importance, in that there are variations in a few aspects of customary views and behaviour, as between one Fore area and another. It should be emphasized that these variations are in a few aspects only, and affect matters of detail rather than those of broad practice. For example, though it was until recently the custom for all Fore groups to practice ritual cannibalism, involving the eating of their own dead kindred, the somewhat elaborate kinship and other rules governing this practice differed slightly from area to area. Thus in the Atigina and Kimi areas I was told that only females and young uninitiated males had the right and duty of eating dead relatives, and that the same rule applied in Wanto'Abarasa, in the latter case with special emphasis on the duties of aged females in practicing this cannibalism of kinship. In certain other Fore areas, however, it appears that the duty of eating various specified portions of the bodies of dead relatives extended to all males and females in the kinship groups concerned.

In the same way, there are differences from area to area in the details of magical practices, including those coming under the heading of sorcery. Belief in such types of sorcery as Tukavu and Kuru extends throughout the South Fore area, but beliefs concerning the necessary techniques vary slightly from one area to another. This, however, does not affect the general South Fore attitude to sorcery, and involves no more than differences of opinion as to essential ingredients (leaves, vines, stones, etc.) required for sorcery rites.

The number of people included in any such Fore Native area is not great, ranging from about 180 in a small area to approximately 1600 in a large one. 1954 census figures for the three areas with which I dealt were as follows:

Wanto'Abarasa	1569
Atigina	1498
Kimi	992

Other South Fore Native areas are as follows: Iagusa, Amusa, Kemo, Ketebi, Mania, Magorti, Ifufurapa, Purosa, Awarosa and Iresa. With the exception of the one local grouping of Karu, in the Native area of Ifufurapa, I did not visit areas other than the three referred to above. (It might be noted that, for census purposes, Wanto'Abarasa is included in the North Fore region, but the division between North and South Fore is one of Administrative conveniences, and does not indicate any distinction in social conditions; such small distinctions as do exist being between the Native areas themselves.

Wanto'Abarasa, therefore, can very well be socially considered, in conjunction with its southern neighbour, Kimi, and Kimi's southern neighbour, Atibina).

Fore Local Groupings

Within each Fore Native area are a number of local groupings, such groupings forming the effective units for political, economic and other social purposes. These are the units which are operative in day to day affairs, the interests and activities of members of a local grouping being closely united in a manner in which those of members of a whole Fore Native area are not. From the point of view of social integration, a Fore local grouping can be considered as comparable to what are called "village" in some other parts of the Territory. However, as Fore local groupings are each composed of a number of territorially dispersed hamlets, the term "village" could not be correctly used for them.

To take the Atigina Native area as an example, this includes seven local groupings as follows: Kamira, Wanitavi, Amora, Wanimkanto, Kume, Okasa and Kasoru. These local groupings vary in size from the smallest, Okasa with a population of 140, up to the largest, Kamira, with a population of 316. Some of the local groupings are made up of members of one clan only; others include members of two or more clans. Okasa, for instance, includes only members of the clan Okasa, while Kamira is composed of members of the clans Kamira and Kutena'visa. In each case the name given to a local grouping is the name of a clan, not of a place. In all Fore local groupings, even those containing comparatively small numbers of people, members are dispersed in several scattered hamlets, to which are given the names of the areas of ground on which they are situated. For example, the hamlet arrangement of Kamira, together with the number of people in each hamlet is as follows:

	<u>Hamlet</u>	<u>Clan</u>	<u>Number</u>
Native Area: Atigina	Apa:Nati	Kutena'vina	35
	Kiarupamenti	"	32
Local Grouping: Kamira	Ara.Vainapinto	"	7
	Wagiri	"	54
	Wai'oti	Kamira	41
	Arinoguti	"	77
	Kudenti	"	70
			<u>316</u>

Distances separating the hamlets in a Fore local grouping range from a few hundred yards up to about a mile. In a number of cases, hamlets are built on sites which appear to have been deliberately chosen for their inaccessability. In this respect there is some difference between the local groupings of Wanto'Abarasa and Kimi, on the one hand, and those of Atigina, on the other. Wanto'Abarasa is in the neighbourhood of the Government Patrol Post at Okapa, and the Kimi area is nearby, while Atigina is more remote. This seems to have had some effect, in that the hamlets of Wanto'-Abarasa and Kimi are often located close to the main road, and are almost

always connected by reasonably good tracks, while those of Atigina are generally remote from the road and are often not connected by cleared tracks at all. Also, there are still hamlets in Atigina which possess various defensive devices against the entrance of sorcery--for example, high palisades with complicated entrances and various "tabu barricades". These are to be seen particularly in the local groupings of Kume and Okasa, where the people openly said that though defenses were no longer usually necessary against physical attack, they are still needed as protection against sorcerers.

However, though the influence of Okapa Patrol Post appears to have been effective in bringing a number of nearby hamlets "into the open", and reducing inter-hamlet suspicion by facilitating freedom of movement between local groups, the belief in sorcery appears to have remained as strong in Wanto'Abarasa and Kimi as it is in Atigina. Particularly is this so in connection with the type of sorcery known as Kuru.

Residence rights in a hamlet and clan membership are determined by patrilineal descent. Marriage is patrilocal, with the usual few exceptions when a husband goes to live in a wife's group.

There is a good deal of marriage between the different local groups, but this does not appear to have had a great deal of effect in reducing inter-group suspicion. For example, in the Atigina local grouping of Kume a noticeably large number of wives have come from the Kimi local grouping of Keakasa, yet Keakasa sorcery is particularly feared by the Kume people. This so much so that Kume men have deliberately obliterated the track connecting them with Keakasa, and openly state the reason for having done so. Visits still take place between the two groups, but are made in daytime by the longer route along the "Government road", and Kume considers itself no longer open to night-time operations by Keakasa sorcerers.

Just as each Fore Native area has its recognized leader or kamintawa, so each local grouping within the areas has a kamintawa, and it is of considerable assistance to a visitor working in the area to win the cooperation of these men. Generally, it is not difficult to identify kamintawa of local groupings in Fore, as care appears to have been taken to select the actual indigenous leaders for appointment as Luluais and Tultuls. If the kamintawa of a Fore local grouping has not himself been appointed to a position of Government leadership, it will usually be found that his son or some other man under his sponsorship has been so appointed. In this way, Fore differs from some other regions in which distinction must be made between Government-appointed Native leaders and the genuine indigenous leaders, and in which it is sometimes difficult for a visiting European to discover the latter.

Fore Sorcery

Though belief in sorcery plays a considerable part in the lives of the Fore, this is not necessarily to say that it has more influence than in the majority of the Territory's localities. In fact, the number of different methods of practicing sorcery is smaller in the Fore than in most other groups known to me. For example, while a comparatively sophisticated people such as the Rabaul Tolai can, even now, name more than twenty different types of

sorcery, careful checking among thirteen Fore local groupings failed to reveal more than six types. And each of the local groupings, without any hesitation, named the same six types.

The Fore have names for ten different types of disease or ailment, which they distinguish from one another. Under some of these names they group more than one kind of disease. For example, both yaws and leprosy are grouped together under the name karu'iena, and both are attributed to the sorcery method which bears that name. Of these ten types of ailment which are recognized by the Fore, four are thought not to be due to sorcery. Three of these cover groups of minor ailments which are said not to cause death. These are as follows:

Nanontana: a general name for headaches and other minor aches.

Nantagavavina: headaches, with vomiting.

Kagai: coughing, which can at times be severe, and has in a few cases been known to precede the death of aged persons. It is not, however, taken very seriously; and the general attitude is that aged persons can be expected to die anyway.

The fourth of these sicknesses which are not explained by the manipulations of Fore sorcerers is korankinu, or dysentery.

Fore views on korankinu are interesting and, I think, may perhaps be an indication that it takes some time for sorcery-explanations of new diseases to be evolved. As far as I could gather, dysentery had become known to the Fore only within the last ten years (perhaps less than ten years). From their experience they realize that it is a very serious illness which has killed large numbers of people, in this way being as much to be feared as the various illnesses which they attribute to sorcery. However, they are still at the stage of simply saying that it is something that "came from Kamano" (the group further north, on the road to Kainantu). They do not believe that any Fore man knows anything about it. Some Fore say that it might perhaps be due to a form of Kamano sorcery, but they are not sure about this. At present, serious though the Fore know korankinu to be, it remains to their minds unexplained.

My view on this point is that, if belief in sorcery in general persists in sufficient strength in Fore, a sorcery-explanation for korankinu will eventually be evolved, and when cases occur they will be attributed to the activities of Fore sorcerers themselves. This may be some indication that kuru, the type of illness and type of sorcery at present most important in Fore thought, has existed in the region for some time--at least for a sufficient period for detailed and widely held views as to its cause to have been worked out.

The six types of sorcery believed to be practiced in the Fore region are as follows:

Karena: In this form of sorcery, a special sorcerer's stone, called nami, is used (the stone is known as nami in the Atigina Native area. In Kimi it is known simply as a karena stone). No tabus are observed by the sorcerer, and no spell is uttered. The stone itself is the sole essential ingredient. Nami stones are said to be full of potency, and can be dangerous to the users themselves, an idea which is in accord with the general Pacific view that stones and other objects can contain continuous charges of "power" (or what is generally called in anthropological literature mana). A nami stone should not be held in

the bare hand, but must be kept wrapped in leaves and handled with tongs made of bamboo. In its use in karena sorcery, a small piece is broken off, pounded to a powder and mixed with the food or tobacco of an intended victim. This leads to severe internal pain, after the food has been eaten or the tobacco smoked. The Fore claim that this is due to "the victim's liver going wrong". Some deaths are said to have occurred as a result of karena sorcery, but many cures are known, both in cases where sufferers have been sent to hospital at Okapa or Kainantu and in those in which treatment has been given by local Fore practitioners. In the Kimi local grouping of Iasui, for example, the Tultul Kiebu and another man named Aiwantaia gave the names of nineteen people they could remember as having died from karena, as compared with eleven remembered cures by local practitioners. The method of cure given was that the following ingredients should be collected (the names are in Fore): karena'igena (a vine); the bark and leaves of takai (a tree); the bark of kau'ia (a tree); and the leaves of kenata (a tree). The first three ingredients are treated and mixed together by the practitioner and then eaten by the sufferer. After this, the kenata leaves are eaten alone. The treatment causes vomiting and, as has been noted, in some cases cures are effected. In my opinion, the name karena is probably used for more than one type of illness, as I have mentioned in referring to Fore sorcery in general. On the whole, fear of karena sorcery does not at present appear to play a very big part in Fore life. The nineteen remembered deaths attributed to it in Iasui was an unusually large number in comparison with the other local groupings with which I was dealing. In some local groupings, the people claimed that they could not remember anybody dying from karena, the whole concentration of thought in such places being on tukavu and kuru, for which lists of remembered deaths were invariably long.

Ka'i: In this, portion of the same nami stone is used, but in practicing ka'i the stone is not placed in food or tobacco. The stone, wrapped in leaves, is held in bamboo tongs and pointed at the intended victim, while the sorcerer calls his name, and calls on the ka'i sickness to enter into him. While in karena an actual poison might possibly be used, this could not be so in ka'i, which essentially resembles the Australian "pointing of the bone". Clearly ka'i is an attempt to explain or rationalize sickness, and perhaps one type of sickness only, since descriptions of symptoms were in this case always more definite and more invariable than in the case of any other Fore sorcery except kuru. Death is said to occur very rapidly after ka'i first becomes apparent. Blood is said to run from the nose, mouth and ears and various parts of the body become swollen, particularly the penis, testicles and legs. The same description was given in all Atigina local groupings, and there was little variation in either Wanto'Abarasa or Kimi. Generally, the people said that if a man started to suffer from ka'i in the morning, he would be dead by sunset. This rapidity of death was to some extent borne out by the case of Inunkaia, a man of Iasui. One Thursday he had visited me at the rest house at Iasui, and later returned to his hamlet. When I asked somebody to take a message to him the following Monday, I was told that he had died from ka'i the previous day. He had become ill only on the Saturday morning, and was dead within approximately twenty-four hours. Descriptions of his symptoms conformed to the general descriptions I had previously obtained: his penis was swollen, his tongue was swollen and protruded from his mouth, his head was twisted to one side, and he could not speak. The people of Iasui said that no attempt to treat him had been made by a local practitioner and that, in fact, no cure was known in the neighbourhood of Iasui. However, in other local groupings I was

told that there were known cures for ka'i. These varied from place to place. For example, an aged man named Nantati, in the Atigina local grouping of Amora claimed that he had been taught an effective cure by a Kume man named Wane. Nantati's cure was to obtain a vine called asana and mix pieces of this with a berry known as u'a and a grass (enani). These were put together in a small slip of bamboo and pushed up the sufferer's nose and down his throat. In the Wanitavi local grouping, I was told that the leaf, not the berry, of the u'a tree was used, and that this was eaten mixed with the bark of the nagaru tree. The Wanitavi people claimed that this cure was invariably effective if the mixture was eaten before the blood had commenced to run from the nose and mouth of the sufferer. They could not remember anybody having died from ka'i in Wanitavi, and claimed that their Tultul, Kuna, and another man, Waruata, had quite recently been cured of ka'i by the local practitioner. Numbers of deaths attributed to ka'i were generally small, the largest number remembered being eight in the Atigina local grouping of Amora, while some groupings such as Wanitavi claimed not to remember any deaths at all from this form of sorcery.

Karu'iena: This is the form of sorcery which is primarily believed to cause yaws and leprosy, though I believe that various types of ulcers and sores are also attributed to it. There was some vagueness concerning the method of practicing karu'iena, but the most general version was that food leavings of a victim should be obtained and wrapped in a special leaf (the name of which I was not able to obtain). This is placed on stones near a fire, the victim's name called, a spell uttered and the karu'iena sickness ordered to go into his body. A cure given in Wanitavi is to obtain the bark of a particular tree (whose name the people claimed not to know), mix this with the leaves of the warebu tree, and rub the mixture on the sores. I was told in most Fore localities that karu'iena was at one time an important form of sorcery, and one much feared. The noticeable success of medical treatment of yaws, however, seem to have altered this situation completely, and karu'iena has now lost most of its prestige and is little thought about.

Kesena: The ailment known as kesena involves aching and swollen joints, but is not thought to lead to death. To afflict anyone with kesena, one places a small amount of ash on a piece of ano (grass), with a twig placed across it. A spell is uttered over this and it is placed on a track just before the intended victim is expected to pass along it. When he steps on or over the arrangement, the kesena sickness goes into his body. Many people claim to know cures for kesena, and these vary from place to place. All, however, involve cutting and/or anointing affected parts of the body. Fairly typical is the cure given me by Kantati of Amora, an elderly man whom I found to be on many points a particularly cooperative and helpful informant. Nantati's cure is to obtain some bark of poia (tree), leaves of kena (a green food plant), the bark of tagai (a vine) and the bark of ivo (a tree). These are mixed with the blood of a pig, cuts are made in the patient's joints and the mixture rubbed into the cuts. Kesena sorcery does not appear to play a large part in Fore thought, though the illness described as kesena is recognized as being extremely uncomfortable and unpleasant.

Tukavu: When one comes to the form of sorcery known as tukavu, one is dealing with one of the two most important forms of Fore sorcery. However, whether or not belief in the practice of tukavu can always be connected with sorcery beliefs or may at times be associated with actual physical violence, remains a moot point, for this is the well known practice widely known in Pidgin in many parts of New Guinea as "shutim nel". The technique is that a victim is made unconscious by physical assault (this is in the case of Fore; in some other parts of New Guinea a victim is thought to be made unconscious by magical manipulation). Long pieces of thorn are then thrust into his elbows, knees, ankles, back, neck and other parts of the body. The thorns work into the body, and the victim is revived, made to forget what has occurred, and sent on his way home. Shortly afterwards, he begins to feel pains in the parts of his body where the thorns have been placed, being particularly affected by the thorn thrust into his neck, since this works its way into his throat and prevents him from speaking or eating. According to the Fore, victims of tukavu have rarely been known to recover and, with one exception, I did not meet anybody in the locality who claimed to know a cure. The exception was an aged man, Barata, in the Kimi local grouping of Keakasa. Barata claimed to have cured a man named Taketo belonging to the same local grouping, and Taketo supported him in this. The method of cure was to obtain the bark of two trees called ikanti and aipewa and mix this with two types of grass, matasa and ioni. To this was added pig's fat and the mixture was given to Taketo to eat. As well, an extremely large cut was made in his abdomen and some of the mixture was rubbed into this. He was able to show me the scar left by the cut, but when asked about marks where the thorns had been supposed to be thrust into his body, he explained that tukavu men are skilled in removing all such marks. He was not willing to name the enemy whom he believed to have practiced tukavu on him. I think it is reasonably clear that beliefs associated with tukavu (as with most types of "shutim nel" activity) are generally attempts at subsequent explanation of an illness which has developed, but that occasionally efforts are actually made to carry out the physical processes of tukavu practices. There have, in fact, been some complaints at Okapa Patrol Post from people who claimed that they had been physically assaulted for purposes of tukavu, but had escaped before the procedure could be carried through. Also, in fact in at least one other region of the Territory (the neighbourhood of Telefomin) it is known that thorns and other substances have been inserted in the victims' bodies, and that at times "shutim nel" has really been carried out. Lists of remembered deaths from tukavu are longer than those for any other ailment except kuru. Such lists of course, probably have little relation to actual happenings, but serve to indicate the place various types of ailments and different sorcery beliefs at present have in the minds of the people.

Kuru: The illness called kuru, and the sorcery beliefs associated with it share with tukavu the main place in Fore thought concerning sickness and death. The means of practicing kuru are best illustrated by describing a specific instance. One of the first kuru sufferers seen by me was Namugoi'ia, wife of Au'ia, Luluai of the Wanikanto local grouping in the Atigina cara. She was trembling spasmodically, and was not able to walk without assistance,

her leg movements being jerky and uncontrolled. Her face seemed to have a rather fixed or "rigid" appearance, and in speaking her words were slurred and indistinct. In discussion with her husband Au'ia, he told me that she had been suffering from kuru for about two months, and that her condition was steadily becoming worse, although she was still being helped down to her garden each day. Au'ia's story was that when he and his family had moved into a new house his wife had left a fragment of her skirt behind. This had been obtained by two men, Iam and Kavarakea of the Kamata local grouping in the Kimi area, both of these men being known to Au'ia as bitter enemies of his. Iam and Kavarakea had taken the piece of skirt back to Kamata, where they wrapped it in a parcel composed of the leaves of the karuku and kigi trees, together with some kigi bark. The parcel was bound with kemkeranta vine. A fire was made and a sorcerer's stone was heated. When the stone was sufficiently hot, the parcel (called in Fore asaina) was placed on top of it. Iam then proceeded to beat the parcel violently with a stick, at the same time calling Namugoi's name, and saying: "I break the bones of your legs; I break the bones of your feet; I break the bones of your arms; I break the bones of your hands; and finally I make you die." After this, Kavarakea threw the parcel into a nearby swamp, where it sank below the mud and water. It was at this moment, according to Au'ia, that Namugoi'ia had commenced to tremble, at first only slightly, but as time went on with increasing violence. As soon as the trembling started, he realized that his wife must have left some personal possession in her former house and that his two enemies from Kamata must have obtained it for use in kuru. His wife subsequently confirmed this by claiming to remember having left a fragment of her skirt in the old house. In this particular instance, the two men, Iam and Kavarakea, were described as being involved in a partnership for the purpose of practicing kuru together, but in most other cases it was thought to be a matter of one sorcerer carrying out the necessary rites alone. Iam and Kavarakea, of course, denied having practiced kuru at all (I met only one man who admitted having practiced it), but Au'ia remained convinced that they were responsible for his wife's illness, and that they were also probably responsible for the death of his eldest daughter, Kima, who had died as a result of kuru several months before. In most kuru cases, it seemed that as soon as the illness became apparent, relatives of the sufferer immediately and almost automatically settled on some known enemy as being responsible. There is, however, a means of divination when uncertainty is felt regarding the identity of the sorcerer. This is to collect a large number of rats, give each the name of a particular local grouping, and then cook them for a fixed period. They are removed from the fire and opened. The rat whose internal organs are least cooked indicates the local grouping in which the sorcerer is to be found. The process is then repeated, on this occasion giving each rat the name of a probable sorcerer in the local grouping concerned, the least cooked rat once again indicating the agency responsible for kuru. It has become well known to the Fore that all methods of sorcery divination are frowned upon at the Administration Patrol Post at Okapa, because they have at times led to physical attack on localities or people believed to be responsible for sorcery. Very few people, therefore, would admit to me that they had carried out divination rites in connection with cases of kuru. Invariably, however, they would give me the name of the person or persons they considered responsible, merely saying, rather vaguely, that they knew "it must be so-and-so because he had always been an enemy".

The people are convinced that there is only one possible means of curing kuru. This is to discover the correct parcel of leaves (asaina), open it and throw the contents into running water. If one discovers and opens the wrong parcel, it is said that one has cured some person other than the one intended, perhaps someone quite unknown to one. This is used as an explanation or rationalization of those instances in which recoveries have occurred without the relatives of the sufferer themselves finding a kuru parcel. In actual fact, extremely few recoveries are remembered. In the local grouping of Wanitavi, for example, I obtained a list of eighty-five names of remembered deaths ascribed to kuru, but only one remembered recovery. In Amora, there were seventy-two remembered deaths, and seven remembered recoveries. In Okasa, I was given the names of seventy-one people considered to have died from kuru, but nobody could remember any recoveries at all. And the situation was approximately the same in other local groupings. As with tukavu, there figures do no more than serve to indicate the position kuru has achieved in Fore thought, particularly since it is now probable that the people are attributing all sorts of deaths which occurred some years ago to kuru. In only one of the few cases of recoveries was an actual claim made that the kuru parcel had been recovered from its swamp, opened and the contents thrown into running water. This was in the case of a man Neni, of Wanitavi. I was told that Neni had suffered from kuru, and that it was generally known that Iaragi, of Kasoru, had been responsible for his illness. Iaragi, however, had relented and had himself recovered the kuru parcel and removed his own sorcery. Later, Iaragi confirmed this, openly admitting that he had practiced kuru and had subsequently cured Neni. (This was, no doubt, a fairly obvious means of enhancing his prestige and standing as a sorcerer). In all other cases of recoveries, it was said that some unknown persons must have removed and dealt with the relevant parcels.

The present position is that the Fore consider kuru to be beyond the scope of European treatments. In this, the kuru situation is different from that in connection with all other types of Fore sorcery beliefs, since people tell of even some types of tukavu having at times responded to treatment either at Okapa or Kainantu. On the whole, the attitude towards kuru is one of resignation and despair. The only sound remedy for this attitude would appear to be that a significant number of kuru sufferers should be cured. I have already mentioned the effect of medical treatment of yaws in reducing the importance of karu'iena sorcery in Fore. A similar reduction of prestige would no doubt occur in the case of kuru beliefs if the disease could be successfully treated. Until that can be done, it seems improbable that any amount of explanation or propaganda will achieve much in removing what is the main cause of suspicion and insecurity in an otherwise unusually harmonious group.

Charles Julius
Government Anthropologist

(NIH)
July 26, 1957

AIR MAIL

Dear Dr. Gajdusek:

Since Dr. Smadel has not yet returned from Europe I am writing to give you the latest developments. This letter will acknowledge receipt of written material accompanying letters from you, dated June 29 and July 10. To summarize other materials received from you to date: a) four brains; b) two cervical cords; c) four sets of tissue obtained in autopsies; d) 36 urine samples; e) 11 rolls of 8 mm film; and f) three strips of 35mm. black and white stills. To summarize material sent to you from NIH: a) 1 16 mm. motion picture camera and case; b) tripod; c) exposure meter; d) 8 100 ft. rolls of 16 mm. color film; e) 4 100 ft. rolls of 16 mm. black and white film; f) 36 one-dozen packages of Keidel-type Vacutainers; and g) polyethylene bags.

You will be happy to learn that preliminary studies on the first brain received from you have revealed degenerative changes in the basal ganglia and, more strikingly, in the cerebellum. The early impression is that there is no acute inflammatory process (including virus infection) although previous infection cannot be ruled out. The group of neuropathologists working on the tissues are starting extensive studies with special histochemical stains, but, as yet, they have not had time to report on these special studies. Also, it is too early to say whether changes found in the first brain will be noted in the brains that arrived subsequently. The fixation of the brains seems perfectly adequate, and the recommendations from the neuropathologists are that you continue to follow the directions supplied to you earlier from NINDB. One of the brains was considerably flattened, however, and they suggest that you take care that the brains are suspended in fixative for at least two weeks prior to their shipment. They do not believe perfusion is necessary. They suggest that the best way to ship the brains is to surround the adequately-fixed brain with formalin-soaked cotton placed inside a plastic bag which is tightly closed to prevent loss of moisture. The bag, with its contents is then surrounded by additional cotton and placed inside a sturdy container of wood or metal. If trace metal studies on the brain tissue are not contemplated, the group felt it would be preferable to fill the outer container with formalin solution as was done with the earlier specimens you sent. The addition of fluid around the bag would give extra assurance that the tissues would not dry out.

We had some difficulty arranging for the copper determinations, but work is now in progress on the samples received from you.

Some of the neuropathologists have read your manuscript with great interest and agree that KURU is a newly-discovered disease of importance. At this time they do not have any comments on the paper, but I wish to point out that it has not been seen by very many of the group as yet.

We have continued to arrange for the development of the films as they arrive and will continue to store, under appropriate conditions, the original negatives and a copy of each print. As regards the prints for the 35 mm. black and white stills, we have arranged for printing as outlined in your directions accompanying the letter dated June 29. We will, therefore, keep on file here in Bethesda the post-card size enlargements of each frame and each film strip. We have also made enlargements for publication as you requested for certain shots taken in black and white. We are sending copies of the enlarged pictures according to your directions.

We are also maintaining files of the material sent us, both the original material as well as duplicate files in NINDB. It would be helpful to us if you can send us material on bond paper, preferably with original typing, since we can then make the duplicate files without having to retype the material. We are, therefore, sending, under separate cover, a supply of bond paper for your use. I realize that it will not always be possible for you to send us original type-written material; however, it would facilitate reproduction of material if you can whenever convenient to you.

We have not, as yet, had an opportunity to see the movies taken by you, but expect to have a "premier performance" of the movie, "KURU," upon Dr. Smadel's return.

We have been notified from the New England Journal of Medicine of the receipt of your manuscript. We have not yet heard of the action taken on it.

Dr. Smadel will return to NIH on August 1. I will call to his attention the developments that have transpired in his absence. I am sure he will write you after he has returned from Europe.

Best wishes from Bethesda for your continuing good work under difficult conditions.

Sincerely yours,

/s/ Carl G. Baker

Carl G. Baker, M.D.
Assistant to the Associate
Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu,
New Guinea)

Enclosures

cc: Dr. Joseph E. Smadel

Carleton:

The pathologists have examined the first brain and found marked degenerative changes in the cerebellum (Purkinje cells and one of the adjacent granular layers); also in the basal nucleus. They are most interested to see whether the other brains, which are being processed, will show the same changes!

Joe

37a appendix

[The New England Journal of Medicine]
July 12, 1957

Dr. Joseph E. Smadel
Associate Director
Department of Health, Education and Welfare
Bethesda 14, Maryland

Dear Dr. Smadel:

Thank you for submitting the article, Kuru....A Localized 'Epidemic' of Chronic Progressive Degenerative Disease of the Central Nervous System in Child, Adolescent, and Adult Natives of the Eastern Highlands of Australian New Guinea, for publication in the Journal.

All papers contributed are carefully considered by the Editorial Board, with the limited available space in mind. You will be notified of the decision of the Board as soon as possible.

Very truly yours,

Joseph Garland, M.D.
Editor

[NIH]
August 6, 1957

Dear Dr. Garland:

I am forwarding correspondence from Dr. Carleton Gajdusek to you which is concerned with his paper entitled "KURU...A Localized 'Epidemic' of Chronic Progressive Degenerative Disease of the Central Nervous System in Child, Adolescent, and Adult Natives of the Eastern Highlands of Australian New Guinea."

Dr. Gajdusek is anxious to add to the manuscript several photographs of patients with the classical attitudes assumed in the newly-recognized KURU.

Prints of pictures which he took were sent to him several weeks ago, and I assume that he will choose the photographs which he thinks best suited and return them to me within the next week or ten days. Should this not come to pass I shall select several photographs from the group suggested by Dr. Gajdusek which are among the materials that we have here in Bethesda.

I trust that you will be patient in your dealings with our colleague who is impeded in correspondence because of his remote location in the New Guinea jungles.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Dr. Joseph Garland
Editor, New England Journal of Medicine
8 Fenway Street
Boston 15, Massachusetts

Enclosure

cc: Dr. Gajdusek

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of New Guinea
[6 August 1957]

Dear Joe,

I suspect that you are back from Europe, and trust it was a valuable and enjoyable meeting. I have not changed my work appreciably in the interval. I am still trying to tie-up our kuru work and leave it in such order that a return in 1-2 years can promise a brief but accurate epidemiological follow-up.

We now have 150 cases of kuru in our study and some 2 dozen or more of our patients have died. Two brains well-fixed in 5% formaldehyde from two of our carefully followed patients were recently posted via air freight to you. Did you get this double shipment along with tissues, both HCHO and Zenker's-fixed, in addition to tissues on an adult kuru, the brain from whom went to Melbourne? In addition I included liver, kidney, spleen from a peculiar kind of cirrhosis we are meeting here. Any pathological comment will be much appreciated.

Naturally I am waiting on pins and needles for any pathological reports from the NIH...but I fully appreciate that neuropathology takes ages!! The immense kuru serum file will soon be sent to you from Melbourne along with Aboriginal and Melanesian blood collections. In the kuru patients immensely elevated beta globulins have been found and this is being further studied. I shall send you a code whereby you can select out classical kuru sera for check on this phenomenon. It must still be fully controlled by checking the normal Fore populace. However, it is a full macroglobulinemia in some cases, and even if present in normal fore is of immense interest. Cyril Curtain at Baker Institute in Melbourne is following this for us. I hope to do more back in the U.S.A.

Another several kuru patients died this week and one, here at our hospital (and a good post was possible). Brain is hardening in HCHO now. Thus, we are getting plenty of pathological material. I only hope that it is the right material, and that neuropathologists and toxicologists will not start saying "I wish I had tissue prepared...." etc. when I finally close down our Kuru Research Center.

Along with this letter is a large shipment of new urine specimens. They are in chemically clean, trace-metal free bottles but have no preservative added, and since not catheterized specs, they are contaminated, undoubtedly. They have been refrigerated since collection, however, and I hope they will stay so in transit. Thus, they are a most valuable collection. Five sets are serial specimens on five kuru patients...all children...treated with immense doses of B.A.L. Some in their first B.A.L. course (Haida'abo and Manne) others in their

second B.A.L. course (Yani) and others in their third B.A.L. course (Nata and Atona). The first specimen is a pre-B.A.L. specimen, and the full time schedules of the protocols are available and will be sent to you. Thus, these specimens are for ashing and trace-metal studies. Especially for copper, mercury and manganese. Manganese looms particularly interesting at the moment, since lengthy reports of manganese poisoning in Moroccan miners present, in somewhat different order and array, virtually every symptom of our kuru patients. We certainly cannot detect any source of manganese or other toxin as yet in our patients and hereditary-familial-genetic factors are holding up well, however, this chronic manganese poisoning in Moroccan miners is the only disease I have yet come across with many of the features of kuru, and it must be seriously considered, in spite of our apparent lack of toxic exposure. We are having soils, house and cooking fire ashes, foods, etc. analyzed for trace metals. Please, Joe, do all you can to have these B.A.L. treatment urine series carefully studied for all heavy metal excretion. We have done the best possible here in the bush to collect them, measure volumes, and keep them trace metal free. In addition, we are interested in amino acid patterns on these patients' urines. If anyone is prepared to do some urine chemistry, in particular, paper chromatography, the specimens could also be used for this. I think only a few drops would be needed and the FIRST...pre-B.A.L....specs on each of the 5 patients would be the ones to use. In addition, I am sending a few other kuru patients' urines...one spec. only...for heavy metal and amino acid studies. These patients are not on B.A.L. or on other courses of therapy... such as Dilantin, Tridione, Cortisone, Benadryl or Testosterone...all of which seem to have no effect on the disease (Asisi, Yosetme, Tovepi = these specs.).

The first 6 reels of 8mm film are here, developed, and I am awaiting a projector and battery with transformer which is being brought in for our viewing of the films. Thank you. Keep the originals and second print on file at NIH. The camera and film you have sent is still at Lae, but I suspect, from your last telegram, that Qantas will now dispatch it to us promptly. They have been trying to collect, and succeeding in collecting too, postage and freight rates from me, the Department of Health, and everyone they can and they completely ignore my explanations that it is all handled by US Government bill of lading. I hope you will get their main office to set a fire cracker under the Lae office.

We can really use the 16mm camera and film and will do our best to get good clinical films off to you. I shall try hard...but it will be my first crack at 16mm photography.

Thank you for your comments on the first draft and for sending it from SCIENCE to NEJM. Please, should you hear from Nejm, assure them that kuru is no figment of my imagination, but a really exciting disease of great importance...for I am sure that is the case. It will be most inconvenient for them to publish long after follow-up papers which refer to their note as the "first report" have appeared. Thus, I am anxious to have word from them.

Detailed epidemiology now fills nearly one thousand cards and I am getting our clinical files...complete charts on all 150 patients, plus the immense epidemiological card file on kuru which represents hundreds of miles of walking and climbing in rugged New Guinea mountains...into good order. They are the total and full record of kuru, and it is these files which I hope to get off to you when I am finally ready to leave. From them we can study all that has been done, all that our laboratory tests have shown, and make all the analyses we wish of kuru. Here in the field I am only trying to keep our records as clear, full and accurate as possible.

In order to complete the one sector of the periphery of the kuru region on our epidemiological maps, I have requested a flight over the unexplored territory south and east of here...the Kukukuku region in general...into which I shall be patrolling in less than a month. Vin and I should make this flight soon...in a day or so if weather permits...to spot and plot out any population centers (villages and hamlets) on the east bank of the Lamari across from our Fore kuru centers on the west bank of the great river whose banks are almost as steep as those of the Colorado at Grand Canyon. Thus, I shall have a Jeep come in for me tomorrow and head out for Kainantu, for the first time in months. We get the plane at Kainantu. Should all go well, and should we not inadvertently pay a call from the sky on the Lamari shore communities, we shall see in a few minutes what we shall spend days and days in climbing and hiking through a few weeks from now. The goal is to place a definitive boundary on kuru and to complete the current epidemiological documentation of the disease, which is now nearly completed.

Thus, Joe, I am still at work but can already see the end of profitable field work on this attack. I hope that kuru has interested you as it has me, for it is certainly a medical oddity and one which bids to give us important information. Should it be genetic, all that it can offer is immediately apparent. Where else in the world is such an illness cause of over half the deaths in an entire race? If it turns out to be toxic or infectious...and for the like of me I can get no leads on this as yet...it is one of the most mystifying and baffling such ailments known! If genetic, the Fore are doomed, I fear! If either, i.e. genetic or some yet undetected toxic or infectious process, medical science has much to learn from kuru.

We have had the director of Psychiatry of the Royal Melbourne Hospital here visiting for a few days and he is baffled as we are. He fully agrees that such a neurological degeneration cannot be a psychosis or an hysterical phenomenon, although there are many things in early cases which lead one to think it that way.

I am completing this disjointed, hasty note from Kainantu.

Specimens, as described, are now being packed for shipment to you. Enclosed also are a few venules of clotted blood which should be adequate for

whole-blood trace metal studies with particular reference to manganese, copper, etc. Also, there are three CSF specimens from kuru patients for similar studies. I send these to you since immense files of trace metal specimens have gone off to Moresby and CSIRO and to Melbourne, and some excitement is being raised already by reports of manganese levels in some of which I am highly sceptical, since there is too much intermediate handling of specimens in other laboratories. These are going directly from patients to you with the hope that someone at the Neurological Institute will have interest enough in kuru to get them into the hands of those who can do trace metal surveys.

The camera, film, tripod and all equipment is now here in Kainantu and I shall sign the receipt voucher and return it to NIH immediately. It looks mighty impressive and I only hope that our results with it warrant the expense. We shall do our best. Kuru is such a fascinating thing to see that our material cannot be at fault...the mountain-stop scenery of our ex-cannibal community is of such grandeur that the background cannot help but impress you. All depends on our ability to master the technical side of the equipment, and we shall do our best. I left our kuru Center with 36 kuru patients currently in the hospital on various unsuccessful therapeutic regimens and I am now again begging for supply for adequate clinical trial of any of the tranquilizers. I read of Serpasil being used in tremors of various types including Huntington's and Sydenhams and Parkinsonism....for we have not been able to get our hands on a single dose. We would need dosage literature along with any drug supply!! B.A.L. we have now used rather extensively without help. Cortisone and Delta-1-hydrocortisone have been hopeless. Testosterone we have only now received in supply adequate to treat two patients on high dosage schedule for a month...and thus far without impressive results. With material on hand, the disease progressing relentlessly to speedy complete helplessness and death before our eyes, the Fore nation in turmoil because of it, and with ritual murders and savage killings in reprisal for kuru sorcery comprising the major administrative problem in the region at the moment, we certainly feel we should be doing more for our patients even if these trials are based on most remote chances of benefit. Administratively we are licked. Sorcery seems as good an explanation for it as any we can offer them. We now see that somewhat over 1% of the total 15,000 population of the kuru-affected region are currently sick with kuru which can be expected to kill them in the next 6-12 months or sooner. The disease is appearing at the same rate and we cannot yet stop any antecedent infectious disease although we have now found cases of undiagnosed acute aseptic meningoencephalitis on whom we are collecting specimens for virus isolation which are off to Anderson in Melbourne, with nothing yet isolated, and serial serum specimens for later serological study. These cases of acute encephalitis or acute aseptic meningoencephalitis are of no detectable relation to kuru thus far, and are unlike any kuru-antecedent symptoms we can elicit or observe. One case with 280 mononuclear cells in the CSF developed in howling friction rub, albuminuria, peripheral edema and everything in the world to fill the bill for clinical "encephalomyocarditis"...although I said in my last

review that it caused no myocarditis in man...and we are still wondering whether he will survive. Thus, infectious disease is proving as interesting as ever here, we are collecting reams of serum and running full blood group genetic studies with Simmons of Commonwealth Serum Labs on all kuru-affected races, but our central problem, kuru, has us licked as thoroughly as EHF had us licked in Korea, I fear.

That this is the best site in the world for study chronic progressive degenerative disease of the CNS at the moment, I am fully convinced. Although I had never any intention of studying this type of disease, the world is beginning to be aware of the necessity for so doing and I have stumbled into the problem. If we can't "crack" kuru with hundreds of cases available for full study in any 3-6 month period, I see little hope for Parkinsonism, Huntington's Chorea, Multiple Sclerosis, etc. etc. Administratively our colleagues are trying to get from Vin and myself advice as to whether to build an immense wall around the fore, and let them die in peace, or whether to encourage "out-breeding" and spread kuru throughout the world. Some decision is obviously needed soon, and I certainly cannot make any.

I do not expect you to study over these long pages with all you must have on your mind at the moment. However, these idle musings may help those few in NIH who have become interested in kuru to know what we are up to and to encourage them to send us ideas, suggestions and requests. So please, Joe, pass this on to any who are involved. Also thank everyone involved in securing the 16mm camera and equipment for us. Today or tomorrow I may be able to get a look at the 8mm films you have returned to us. There are 6 reels here. In addition, there should be some later, additional reels now in your hands. I hope they have arrived. Finally, we have dug up our first film attempt which is important in that it shows many of our early cases in the early stages of the disease depicted as much further advanced on these later reels. Many are now dead.

If your photo labs can handle any of the printing I have requested we shall be most grateful. I am getting a map off to the NEJM for the paper they have... in case they decide they might like some cartographic localization of this entity...and I leave it to you to select from the black and white negatives now in your hands any photos of kuru strabismus, flexed posture, or facies to submit to them. Copies sent to me will immediately be captioned and captions returned to the Journal. If, however, it is too late to illustrate this first report, well and good. We shall use illustrations for the second paper off to the Australian Journal. I do not want to hold up the NEJM article at any cost!

Detailed epidemiological cartography is our current problem, and I hope to have that handled and discussed in our next report.

A copy of this letter will be sent to Dr. Rivers and NFIP and I shall try to keep him informed of what we are up to. Needless to say his grant is all that makes this "unsalaried year of investigation" and I shall be back in the U.S. a pauper.

Our genetic study of Cape York aborigines is off to the American Journal of Physical Anthropology. The New Guinea and New Britain genetic studies are soon to go off---some of last year's "side work"---and my report of skull flattening of infants in New Britain and its lack of effect on growth I hope to get off shortly. However, the matter of immense importance to me, the series of definitive papers on our AICF test...on which several other groups, including Sir Mac himself...are basing studies now in press, which is in hands of AMA Archives of Internal Medicine and which fully documents what I briefly discussed in my recent paper in NATURE, is still unsettled. I certainly hope that Journal gets to work on them!!! They are a set of papers of which I am proud and I do not need their editorial comments to tell me whether they are good or not! They are!

Sincerely and gratefully yours,

/s/ Carleton

Carleton

AUGUST 13, 1957
[NIH, Bethesda, Md.]

DR. D. C. GAJDUSEK
C/O DR. V. ZIGAS
OKAPA PATROL POST
VIA KAINANTU
EASTERN HIGHLANDS
TERRITORY OF PAPUA AND NEW GUINEA

PRINTS OF STRIPS ONE AND TWO AIR MAILED YOU TWENTY-SIX JULY STOP
NO OTHER STILL FILM RECEIVED STOP YOU SELECT AND FORWARD PRINTS
TO AUSTRALIAN JOURNAL STOP IDENTIFY FOR ME PRINTS FOR AMERICAN
ARTICLE STOP I WILL FORWARD THESE STOP

JOSEPH E. SMADEL, M.D.
ASSOCIATE DIRECTOR
NATIONAL INSTITUTES OF HEALTH

(NIH)

August 16, 1957

AIR MAIL

Dear Carleton:

I had a very fine time in Europe, a good meeting for a week at the Poliomyelitis Congress in Geneva, and then a good touring vacation in Italy. I got back the first of August, but I am now off for a one-week's visit to the Rocky Mountain Laboratory.

I read your correspondence on my return including the two most recent letters describing your proposed trip around the periphery of the area occupied by the Fore people and the one which arrived yesterday going into detail about the photography.

One thing begins to worry me a little more than before. What will happen to the records, the material, and the information you carry in your head if the plane comes down in the jungle or if one of the indigenes decides to revert to cannibalism? I think you better finish up the work cautiously (as regards your own well being) and get the hell back here. It seems to me the simplest procedure for keeping you in one place long enough to analyze all of the data and to write the papers is to put you on as a Visiting Scientist for some months in the Institute of Neurological Diseases and Blindness. This will serve the added purpose of buying time while you decide what your next task should be. I would strongly recommend that you stay home for a year or so and fully recover from your tripping.

Dr. Ness has done a number of copper determinations on the urine specimens. Enclosed are some of the values. While certain of the determinations are higher than the usual normal, the group here is unable to give you any definitive interpretation at this time.

All of the shipments mentioned in your letters have been received. This includes the two lots of urine and the six brains.

Additional histological sections have come through, and the boys are excited about the diffuse degenerative involvement which goes far beyond the cerebellum. A note from Dr. Klatzo is enclosed. Since I am leaving before I have a chance to read the typed version of this I don't exactly know what Klatzo will have to say. In case he doesn't

mention it in his note, he requested the following sometime ago:

1. "Send more autopsies of spinal cords."
2. "Send histories of patients from which autopsies were taken--histories that were sent do not match autopsies."

Dr. Shy says he can recall no other lesion with such acute destruction of the nerve cells and associated neuronophagia. At the moment the inclination is to attribute it to a toxic effect. Shy says that the lesions in the somewhat similar disease found in minors connected with magnesium are more limited in their distribution than in KURU, i.e., in the magnesium malady they are essentially limited to the basal nuclei.

I haven't the foggiest idea what has happened to the prints we sent you on the 26th of July. It is apparent from even your most recent letter that you have not yet received them. I cabled you August 13 to look for them. Maybe they are lost in the jungle.

Very best.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu, New Guinea)

Enclosures

From Dr. Klatzo 15 August 1957

Preliminary Findings in Brain of Patient YABAIOTU, 50 year old female

GROSS: Marked engorgement of veins over the hemispheres. Coronal section reveals 3 x 4 cm in diameter area of hemorrhage in the white matter of the left occipital lobe. Vascular channels throughout the brain dilated and on few occasions surrounded by petechial extravasations into the parenchyma.

MICROSCOPIC: Cervical Segment of the Spinal Cord: Symmetrical demyelination in post. spino-cerebellar tracts, less intense in ventral spino-cerebellar. Some anterior horn cells show chromatolysis or vacuolation of cytoplasm.

Medulla: Demyelination in spino-cerebellar tracts. Many cells of inferior olives show disintegration, chromatolysis or vacuolation of the cytoplasm. Marked astro and microglial response in the inferior olives. Nerve cells in hypoglossal nucleus, vagus, n. cuneatus show frequently degenerative changes of various intensity.

Pons: Degenerative changes of rather acute character are found in various pontine nuclei.

Cerebellum: There are striking changes affecting Purkinje cells. There are numerous "torpedoes" (Ballooning of the Purkinje cell axons) and bizarre deformities of Purkinje cell dendrites. Numerous round or asteroid bodies are present, which are brightly anisotropic in polarized light. These probably represent neurofibrillary degeneration of Purkinje cells. Granular layer of the cortex is occasionally rarefied. Very numerous fat-containing reactive microglia in both molecular and granular layers of the cerebellum. In the dentate nucleus neurons show degenerative changes. Terminal nerve fibers show degenerative bulb formation and scavenger activity of microglial cells.

Basal Ganglia: Substantia nigra shows degeneration of neurons. Numerous reacting microglia cells are distended with melanin, which undoubtedly was picked up from the dying nerve cells. Caudate, putamen, pallidum show advanced degeneration of neurons. Very spectacular neuronophagia of the nerve cells in the caudate. Thalamic nuclei show less intense changes in the neurons; on the other hand there is very intense gliosis affecting predominantly the medial nucleus. Hypothalamic nuclei including mamillary bodies show marked glial response, neuronal damage is less intense.

Cortex: Including Ammon's Horn show relatively little pathology with only occasional hyperchromatic or tyrolytic cells.

No inflammatory changes can be found throughout. Only few vessels in the inferior olives contain lymphocytes in the Virchow-Robin spaces. This can be easily explained as secondary to the degenerative changes.

Impression: The above mentioned findings do not give any ground to suspect infectious or inflammatory process. The widespread involvement of various structures does not fit into any of the known hereditary degenerative patterns. Toxic etiology of the condition appears to be most likely. Nutritional factors may be involved in producing toxic metabolites.

OFFICE MEMORANDUM • UNITED STATES GOVERNMENT

TO : Associate Director (Intramural Affairs), NIH DATE: August 8, 1957
FROM : Acting Director, NINDB
SUBJECT: Kuru

Before Dr. Bailey left, he asked me to follow up the work on Kuru with Dr. Gajdusek. We have worked through Dr. Baker on this and a summary report of all activities is attached for your information.

We have put together six reels of film into a twenty minute movie. This shows the type of jungle in New Guinea, the natives, and about half of the film shows various patients afflicted with this neurological disorder. We shall be glad to project this film for you at your convenience.

Pathological studies of four brains show most of the damage in the cerebellar region. Dr. Shy is convinced that Kuru is not Wilson's Disease.

This report has been presented to Dr. Masland. He believes that both the speed with which the disease develops and the wide range of age groups affected offer evidence against a diagnosis of hereditary ataxia.

He suggests that it might be of toxic or deficiency origin. For example, it is known that various tapioca plants differ in the amounts of cyanide content, that preparation of native food may not eliminate this poison, and that demyelination can be produced by chronic cyanide poisoning.

Because no indications of an inflammatory response have been found, an infectious disease seems to be ruled out.

Blood tests for the presence of parasites should be undertaken, if not already done. Chromatography or electrophoretic studies of the blood might provide a clue.

The most important problem is the need for an epidemiological study, with experts in anthropology, genetics, diet and personal habits, and water supply collaborating as a team.

The reports on the pathology found in four brains to date will be sent to you soon.

Dr. Masland will be in Bethesda on Wednesday, August 21, 1957, if you wish to discuss Kuru with him.

Henry A. Imus

Attachment

KURU

Kuru is a localized progressive degenerative disease of the central nervous system, occurring at any age in certain groups of natives, predominantly female, of the eastern highlands of Australian New Guinea. It resembles the heredo-familial neurological disorders, such as cerebral ataxia, paralysis agitans, and hepatolenticular degeneration. However, reflex patterns are usually normal, and there are no sensory changes or systemic involvements. It is rapidly fatal, rarely lasting over one year.

No gross pathological lesions have been found, even in the brain, and chemical tests have yielded no information as yet.

All treatment thus far has been ineffective in altering the course of the disease. Non-addicting analgesics, sulfonamides, antibiotics, adrenal cortical steroids, anti-histamines, anti-convulsants, nutritional factors or BAL have been tried with no success.

Transactions with Dr. Gajdusek:

1. Correspondence apparently began before 1 May 57.
2. 1 May 57--Brain handling instructions sent to Dr. Gajdusek.
3. 7 May 57--Summaries on Wilson's disease sent to Dr. G. by Dr. Bailey.
4. 6 June 57--Approximately 35 urine samples received by NIH, sent by Dr. G. on 28 May 57.

Six rolls of 8 mm. color film to be developed and copied were received around this date, sent by Dr. G. on or before 28 May 57.

5. 9 June 57--Small pathological specimens from Dr. G. first autopsy of a Kuru patient, male child, had been received and examined. Brain and major portions of viscera had been sent to Melbourne.
6. 18 June 57--Received from Dr. G.:
 - a. Manuscript on Kuru
 - b. History of a woman Kuru patient autopsied
 - c. Complete autopsy material, including brain, from the woman above.
This is the first brain sent by Dr. G. to NIH.
7. 25 June 57--Letter from Dr. Smadel to Dr. G. acknowledges receipt of items mentioned in #6 and the films. Studies on chronic cyanide poisoning sent to Dr. G.

8. 7 July 57--The following equipment was shipped to Dr. G. from NIH:
 - a. 1-16 mm. motion picture camera (Bolex H-16) with case.
 - b. 1- heavy duty tripod
 - c. 1- exposure meter
 - d. 8- 100 ft. rolls of 16 mm. color film
 - e. 4- 100 ft. rolls of 16 mm. black and white film
 - f. 36- one doz. pkgs. of Keidel-type vacutainers
9. 8 July 57--Received from Dr. G. (sent 29 June):
 - a. Autopsy material from two female Kuru patients
 1. two brains
 2. one complete post
 - b. Histories of these patients and others
 - c. Two rolls of 8 mm. film
 - d. Three strips of 35 mm. black and white stills
10. 15 July 57--Sent to Dr. G.
 - a. First six reels of developed film
11. 23 July 57--Received from Dr. G. (Sent 10 July):
 - a. 1 brain
 - b. 2 cervical cords and 1 pituitary
 - c. 2 sets of autopsy material other than CNS-Formalin fixed
 - d. 2 sets of autopsy material other than CNS-Zenker's fixed
 - e. 1 manuscript - "Kuru - Clinical Study of a New Paralysis--Agitans-like Syndrome"
 - f. One history
12. 26 July 57--Sent to Dr. G.
 - a. Black and white prints of 35 mm. film sent to NIH on 8 July
 - b. Bond paper
 - c. Letter from Dr. Baker summarizing materials received from Dr. G. thus far
13. 29 July 57--Received from Dr. G.

Telegram requesting help on freight problem
14. 30 July 57--Sent to Dr. G.

Telegram in reply to one of previous day
15. 31 July 57--NIH

Showing of first six reels of film sent by Dr. G. Drs. Masland, Sarason, Gladwin, Shy, Klatzo, Dastur and Ness attended

16. 2 August 57--Received from Dr. G.

- a. 2 brains
- b. One set of autopsy material other than CNS-Formalin fixed
- c. One set of autopsy material other than CNS-Zenker's fixed
- d. Liver, kidney, spleen - Formalin fixed - case of cirrhosis?
- e. Liver, kidney, spleen - Zenker's fixed - case of cirrhosis?

Summary of specimens, material, etc. sent or received to date (5 Aug 57)

1. Received by NIH:

- a. 6 brains
- b. 2 cervical cords
- c. 8 sets of tissue obtained at autopsy (some sets duplicated when sent in another fixative. These were not counted as additional sets.)
- d. 36 urine samples
- e. 11 rolls of 8 mm. film
- f. 3 strips of 35 mm. black and white stills
- g. 2 manuscripts

2. Sent by NIH:

- a. 1 16 mm. motion picture camera and case
- b. 1 tripod
- c. 1 exposure meter
- d. 8 - 100 ft. rolls of 16 mm. color film
- e. 4 - 100 ft. rolls of 16 mm. black and white film
- f. 35 one doz. pkgs. of Keidel-type vacutainers
- g. polyethylene bags
- h. developed film from the first 6 reels sent by Dr. G.
- i. black and white prints of 35 mm. film sent by Dr. G.

[Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea]
16 August 1957

Dear Joe:

Immediately upon the heels of the last verbose letter, another. We have rushed through two hundred feet--two reels--of Kodachrome on the new camera, and are rushing them off to you in the hope that they can be urgently processed and a telegraphic report sent to us, as to whether we are recording anything or not. I am a complete novice with this cine machine, but have tried my best. We had a special group of kuru patients on hand, and these I have briefly surveyed. Furthermore, on the tail end of the final film is a Congenital Tremor, which is another interesting "new" disease (in Melanesians, at least) which must be differentiated here from kuru. Perhaps the few seconds' comparison are enough to show the difference. If we are doing O.K. with the equipment, I can then promise you a complete clinical documentation of the toe grasping, posturing, reflex patterns, emotionalism, etc., and full comparisons with the hereditary, familial congenital, non-incapacitating and non-fatal tremor which is found--but rarely--hereabouts. This too we shall report in our next kuru paper.

Acute lymphocytic meningoencephalitis is upon us. We now have a total of five cases with a CSF pleocytosis, fully mononuclear, and unrelated to mumps epidemics or any other cause of benign aseptic meningoencephalitis of which I know. Whether to call the cases encephalitis or not, is a problem. Four of them would better qualify as mild encephalitides. Two, in today from the same village, have 1200 cells (96% mono's) and 550 cells (100% mono's) per mm³ of CSF, respectively. They are two girls who show lassitude, painful neck and head which has just subsided (but no true meningismus, for there is not a positive Kernig or Brudzinski) and marked wasting. I did LP's, more on the basis of their behavior than on the basis of meningismus. We see plenty of the latter, for H. influenzae and N. intracellularis meningitis are both still with us at Moke-Pintogori. Both fluids were cloudy, the first markedly. Differential counts were checked by direct chamber differentials, using acid and stain and dried and stained smears of the CSF. If they follow the course of the former three proved cases, they will slowly start to eat again and then regain the lost weight--which is considerable. In addition, two other patients came in with obviously the same syndrome, but so late that I could no longer find cells in CSF....Pandy's were slightly positive and full CSF chemistry reports are not yet back to me.

However, Joe, these cases bear no relationship to kuru that we can detect. All kuru patients are well nourished and show none of the cachexia and weight loss, and obvious acute recent illness, of these meningoencephalitis patients, and kuru patients and their relatives deny emphatically any disease similar to these newly discovered cases, even when we bring them to see them. We cannot thus far establish any link, whatsoever, between kuru and this acute CNS infection that we have found in the region, certainly five times, perhaps seven, now. Kuru, on the other hand, is not rare, but is occurring constantly. New cases appear every month; our first estimate that one percent of the affected populace was currently dying rapidly of kuru was conservative, and we know now that there are over 150 cases among the 15,000 natives.

In the box containing the first two reels of 16 mm cine film, is a developed reel of Kodachrome 8 mm cine film. This was our first kuru film, which I took on a borrowed 8 mm Kodak "box-Brownie-type" cine camera. It is far better than the subsequent six reels of 8 mm cine film our guest Smythe took, and which you have developed and sent copies to us. It shows kuru well and I urge you to study it if you have the time. An accompanying sheet summarizes the contents of the 8 mm cine films you have received. The current developed film--the first--is given the number 0. Then, I have renumbered in proper sequence the first six 8 mm films you had developed and copied, and I beg that you have whoever is looking after them renumber them as indicated on the accompanying sheet, which is a brief "contents table" to be used later in editing an 8 mm kuru film. We obviously have enough, in spite of the two initial very poor "travelogue" reels that Smythe apparently included, to make a really good presentation of kuru on 8 mm already. Since the date of this new first reel (number 0) was early April, we have in the series pictures of the progression of the disease in individual patients. Many pictured in the first reel have already died or are now terminal cases, with less than a month of life expected.

Important Note: In addition to telegraphing us information about whether our first two reels of 16 mm are a success, and if not, what to do, please advise us as to whether we should shift from standard "silent" 16-frames-per-second to 24-frames-per-second, which is required, I believe, if a soundtrack is to be attached. Since it might be well to plan on a later sound track (we can get tape recordings of the foolish laughs, dysarthria, echolalia, etc., along with plenty of background sounds, to boot), I have wondered whether we might not use 24, rather than 16, and plan definitively on sound projection later. If so, I would like concurrence from you in NIH and we shall promptly switch all our shooting from 16 to 24 frames per second. We have plenty--really plenty--of some of the best cine clinical material in the world. With almost 150 active cases on hand to study, all stages of reflex patterns, tremors, emotionalism, incoordination, posture maintenance, ataxia, etc., can be shown in detail, along with studies of our acute encephalitic cases, and of the differentially diagnostically important congenital tremors who are really different, as I hope you will see in film II, and those who do not rapidly deteriorate and die.

Also in the box with the 8 mm film "O" and the 16 mm films I and II, are five developed rolls of 35 mm Leica still film in black and white. These contain some of our most valuable kuru documentation, and illustrations of publications will come largely from these. They are unreplaceable films, for they show stages in patients pictured earlier and subsequently, and they show many patients in their native village settings as we discover them on arduous patrols. Please, Joe, can we beg to have these five rolls printed carefully into prints approaching postcard size for file copies, from which to select publication frames. If such a set of prints were sent to us here, as we are hoping will be the case with the three previous rolls of black and white still film I sent to you, we can select, immediately, appropriate frames for the two publications in press. If you will take the responsibility for so doing for the NEJM paper and send us copies of what you select, we can check what you have selected for accuracy and promptly slip in captions.

Summary sheets summarize the contents of these five rolls of black and white still film (35 mm), which are films numbered 4, 5, 6, 7 and 8, now in your hands. Films numbered 1, 2 and 3 had been shipped much earlier.

Finally, Joe, I must beg your pardon for all this detail. I hope someone at NIH is interested enough in kuru to be willing to take these pleas off your hands, study them and work through a few for us. We know we have unusually good material on hand, Joe, and our study will be reasonably thorough before we terminate it in September or October. Thank you again for all of your help and patience.

/s/ Carleton

Purosa--South Fore
On Patrol
25 August 1957

Dear Joe,

We are patrolling, finishing up Kuru Epidemiology, and have just shot films of a group of 8 Kuru patients found in this region. Thus, a series of 8 rolls of Cine film are already off to you (some should already have been received). We are awaiting telegraphic report on whether we have been leaving the lens cap on or some other fool thing. Any comments on technique, improvement in material or photographic technique will be much appreciated.

Enclosed are protocols of the last 3 films...copies were also sent with the films and in previous letters the earlier films were abstracted.

We shall use up the remaining film on kuru in the next few days, and since it behooves us to try to film more of the interesting congenital tremor we have discovered here and of the encephalitis patients as well as the Kuru, and since, once we know of our technique, we wish to try to get some valuable close ups of toe movements, stability tremors, and of reflex patterns, etc. As well as further shots of kuru in the native setting, we could really use further film. If the National Institute of Mental Health and Blindness can see to agreeing with us from the material on the first 8 rolls now en route to you and the next four coming, please tell them to rush to us further film...particularly Kodachrome since light here is usually too bright for Tri-X with our available filters....and we shall do our best to improve and correct anything that they suggest we do. We have a great deal more to show and to study on film!

An extensive patrol into uncontrolled Kukukuku territory is to start in early to mid-September (probably on Sept. 10-15), and if any film can get to us by then, we shall be most happy for there may be much worthy of medical documentation on that trip.

If further Tri-X film is sent, would you ask the NIMHB group to also send us the appropriate gelatin filters, as suggested on Tri-X film-instruction sheets. These are:

Kodak ND-3
Kodak Wrattan Filter X2
Kodak Wrattan Filter G
Kodak Wrattan Filter A

All goes well. A third report on kuru with much additional material has been sent to Klinische Wochenschrift. We are hoping to get Kodachrome films and plenty of black and whites published with it. The Medical Journal of Australia has accepted without change our second paper and I am hoping---as I have said before---that the NEJM will come out first with the first report of the disease, written 2 months earlier. I am

awaiting arrival of the prints (glossy-enlarged) for the Australian Journal article and when we get them I shall write captions and rush them to them. They have agreed on 8 pictures!! Perhaps one of the kuru hospital or the patients seated about outside of it might be included. The others could best be of patients of different ages and sexes in different stages of the illness. For the NEJM I leave the selection of the best 2 or 3 pictures you can find in the 5 odd negatives I have sent you, to you.

The NFIP asked for the first paper to be included in its collected papers and I have already forwarded the reprint order they sent me to the NEJM. I trust the further report in the Australian Journal will also interest them. I have no comment on the second manuscript yet from you or Dr. Rivers. The much longer and informative third report I have already sent to the Journal and as soon as I get back to civilization--i.e. our Kuru Center -- I shall mail copies out to you and to Dr. Rivers. Our Kuru case series will shortly exceed 200 cases and in the group we shall shortly have over 50 already dead from Kuru and over a dozen brains have been obtained. Two on children are waiting to harden before I send them to add to your kuru collection. A further brain collected in special trace-metal free formol-saline in a special plastic box (trace-metal free) is hardening also. Would there be trace-metal chemists about who might study this unique specimen thoroughly along with thorough neuropathology if I send it to you?? We do not know whether the Melbourne crowd can dig up the proper studies for it and thus would like to know if there are those at NIH who would really settle the matter. It has taken a great deal of work to get such a specimen!

I have already had rather extensive trace-metal work on blood done, and although it is not definitive, now manganese and copper are being again suggested---although I am sceptical!---by our chemists. The immense file of CSF specimens from KURU for trace metals has stood about in a Moresby Ice Box unstudied, and I have thus asked for the entire series of CSF's in trace-metal free containers to be forwarded to you and have sent a few others directly to you. These obviously are sufficient to settle the matter once and for all as to whether SF has any trace metal in excess if there is anyone who can do the study...perhaps both a spectrophotometric screening and an analysis for anything that shows up.

With the September patrol of about 1 month, I hope to wind up this first field-attack on kuru. Our estimate that 1% of the entire populace are dying each year of the disease is now known to be low, and probably somewhat over 150 active cases are about the kuru region at any one time. We have not yet had them shoot at us, although they are not always very intrigued by our studies and tell us so in no uncertain terms. A patrol was attacked just within our region a few weeks ago, and we are hoping not to encounter any of the same in our work. Thus far, our Fore and their kuru-affected neighbors have been fine patients with a greater tolerance for our investigative mien than many a Western group----but

they know full well that it's all sorcery and that it is best to humour our scepticism. Murders in reprisal for kuru sorcery are now rivaling the Kuru cases in number in some regions and thus kuru plus kuru reprisal murder form some 50-75% of deaths, at least, in many regions and, should we add to them the infants who die when their kuru afflicted mother leaves them behind, we would find, I fear, that the Fore never die at all---were it not for kuru.

Enough for this note. I have pig fat rubbed all over me from admiring observers who have never before seen a typewriter---most with great pig-tusks through their noses--and I am hoping that one of them, in carrying the films and this letter to Moke will not open both and inspect the contents with pig-grease covered hands.

Sincerely,

/s/Carleton

Carleton

The AMA Archives papers on AICF test are now accepted--unchanged. I am quite pleased. Sir Mac came out in Nature with a "follow-up" already.

Carleton

BLEEDINGS done 22 August 1957. On important kuru-non kuru border of Fore (Agakamatasa) and Kukukuku, across the Lamari River. Specimens for serum file and for blood group genetics on clots and hemoglobin

117. Karame'o	M 15	Kukukuku	Simbaria
118. Mungarao	M 13	Kukukuku	Moraei
119. Parawetomo	M 13	Kukukuku	Moraei
120. Uwiwaritmo	M 13	Kukukuku	Moraei
121. Azibara	M 12	Fore	Agakamatasa
122. Pagirodumu	M 12	Fore	Agakamatasa
123. Eruwaza	M 18	Fore	Agakamatasa
124. Avegaia	M 16	Fore	Agakamatasa
125. Kugumpa	M 17	Fore	Agakamatasa
126. Mmaivana	M 9	Fore	Agakamatasa
127. T/T Kure	M 25	Fore	Agakamatasa
128. Paritai'o	M 15	Kukukuku	Moraei
129. Agurio	M 15	Kukukuku	Moraei
130. Waianu	M 10	Kukukuku	Moraei
131. Aveia'Weno	M 25	Kukukuku	Moraei

MAIL to:

Lois Larkin and/or Dr. S.G. Anderson
Walter and Eliza Hall Institute of Medical Research
Royal Melbourne Hospital P.O.
Melbourne, Victoria

24 hour urine on TOVEPI vol. 1,020 ml with 50 ml 20% HCl added.
24 hour urine on ATOGORI 370 ml with 50 ml 20% HCl added.

[The National Foundation for
Infantile Paralysis]
August 5, 1957

Dr. Carleton Gajdusek
Okapa Patrol Post
via Kainantu
Eastern Highlands
Territory of New Guinea

Dear Doctor Gajdusek:

Thanks for your letter of June 29th with a copy of a letter to
Dr. Joseph E. Smadel and a copy of a paper on KURU which you propose to turn
in for publication.

I am glad to hear that things are going all right with you, even though
your task is somewhat difficult at times.

The paper which you propose to publish is good and I would like to know
where you intend to send it for publication. I have asked Doctor Kumm to have
you order reprints, at our expense, in case the paper is accepted for
publication.

It certainly looks as though you are dealing with a genetic disease.
However, I think you ought to seek very carefully for some environmental factor
peculiar to the Fore people. For example there might be something peculiar in
their diet or something taken at ceremonial rites. This is all I have to
suggest.

Best of luck.

Sincerely yours,

Thomas M. Rivers, M.D.
Medical Director

cc: Dr. Joseph E. Smadel
Dr. Henry W. Kumm

(NIH)
August 30, 1957

AIR MAIL

Dear Carl:

Just before I left last week for a visit to the Rocky Mountain Laboratory, Dr. Leonard Kurland, Chief of the Epidemiology Branch, NINDB, came over to inquire about the KURU study. He was particularly interested in the possibility, re-emphasized in the last few weeks by the pathological findings, that KURU resulted from some toxin, and he was opposed to the idea of it being dependent upon genetic factors. I asked him to read your manuscript and to let me know what he thought might be done to further the work. Attached are his comments as well as certain information on cycad nuts, prepared by Dr. Whiting. I think you will find Kurland's remarks stimulating and probably helpful even though you will recognize sentences which are probably unduly dogmatic and undiplomatic. Nevertheless, with the good and bad, I am sending the material to you in toto because I do not wish to lose any of the flavor in abstracting the material.

Attached to Kurland's correspondence is a covering note by Dr. Imus which contains the sound suggestion that plans for future studies of KURU be held in abeyance until you get back here to go over all of the material and to discuss the problems at length with various members of the staff of NINDB.

Yesterday I sent you a copy of my letter to the editor of the New England Journal of Medicine. I did not add a P.S. to the effect that the editors gave reasonable assurance that the article would be accepted and would probably appear in an issue in November. I am going to have trouble picking out the still pictures for illustrations, particularly in writing legends for the damned things. I had hoped by this time to have had a reply from you indicating which ones you wanted used and giving the appropriate legends. Since your last messages failed to mention the receipt of the stills, I assume they must be lost some place on the jungle trails. Unless I hear from you within the next week, I shall choose the pictures

and write the legends, so just don't bellyache about the results.

Last week we received the following from you: five 35 mm. developed still film; one 8 mm. developed cine film, two 16 mm. undeveloped cine films, and one 100 ft. roll of 16 mm color film.

I am not sure whether I am going to the Bangkok meeting in November. At the moment, I think the odds are against it. I think you ought to get home, and I would suggest that you skip consideration of Bangkok and also shorten or eliminate your proposed visit to Kuala Lumpur.

Best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M. D.
Associate Director

Dr. D. Carleton Gajdusek
Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea

CC: Dr. Imus
Dr. Kurland

43a enclosure

OFFICE MEMORANDUM - UNITED STATES GOVERNMENT

To: J.E. Smadel
Associate Director, NIH (Intramural Affairs)

Date: August 26, 1957

From: H. A. Imus
Acting Director, NINDB

Subject: Kuru

Attached is a review of subject neurologic disorder which was prepared by Dr. Leonard T. Kurland, Chief, Epidemiology Branch. This report discounts possible genetic factors, and suggests a toxic origin.

Dr. Richard Masland has been kept informed of all of the details of Dr. Gajdusek's study. He suggested on July 31, 1957, that Kuru was probably not hereditary but due to a toxic or deficiency problem in New Guinea.

Before committing NINDB to any participation in investigations in the field, as suggested by Dr. Kurland, it seems desirable that both Dr. Bailey and Dr. Masland have an opportunity to discuss the problem with Dr. Gajdusek as well as with other members of the NINDB staff.

Henry A. Imus

Attachment

I appreciate the opportunity of reviewing the report by Zigas and Gajdusek and Gajdusek's correspondence on Kuru. The difficult conditions under which they are working probably account for the trend the research has taken, for it is clear that additional epidemiologic study would be more productive than their time-consuming therapeutic and repetitious clinical descriptive efforts.

I seriously doubt that this can be a genetically determined disorder. There appears to be a geographic focus and a high degree of familial aggregation of cases but some condition related to environment common to these families will, I predict, be found to account for such focalization of cases.

I find the genetic hypothesis difficult to accept for the following reasons:

1. If the assumption that the disorder is new--20 years or so in this area--is correct, it is practically impossible to explain the extremely high gene frequency (at least 25%) in this population of 10,000. For this to occur, there must have been, in a recent generation, an enormous spontaneous mutation rate for a specific gene. This would have to be in terms of several per cent instead of the usual 10^{-5} or 10^{-6} mutation rate.
2. If the assumption that this is a new disease is incorrect, it would still be highly improbable that such a gene frequency could ever develop in view of the very serious reproductive disadvantage present in the affected as compared with the unaffected in the population.
3. The age distribution is from 4 to 5 years of age throughout adulthood. The upper limit is not given. Although many hereditary disorders of the nervous system have an appreciable age span such as through childhood and adolescence or throughout adulthood, it is unusual to find a single genetic form (recessive or dominant) spread over childhood, adolescence and adulthood.
4. The sex ratio differs for children and adults. I am not aware of any hereditary disorder due to a single genetic form (recessive or dominant) in which the sex ratio changes from slightly more than 1 to 1 in children to 13 to 1 in adults. If Dr. Gajdusek's observations on sex incidence in the population are complete, this odd sex ratio is very much against a genetic mechanism. (A similar preponderance of males (12 to 1) for lathyrism is of interest in this respect.)
5. The occasional case in a non-Fore woman now living in the Kuru area cannot be passed off lightly and is very strong evidence for a non-genetic mechanism.

6. Most geneticists do not believe in "anticipation" as described here. One would expect no offspring from affected children in an earlier generation. Obviously, some cases occurring in the present generation with the wide age distribution described will be in children whose mothers (affected or not) at least had to reach maturity.

7. A characteristic of most neurological hereditary disorders is that they selectively affect one or only a few of the central nervous systems (motor, cerebellar, or selected portions of the basal ganglia, etc.); the diffuse involvement of almost the entire central nervous system found in the case described by Dr. Klatzo of NINDB is not characteristic of a genetic disorder.

The data on age and sex reveal a selectivity for women and children. I am not acquainted with any such sex ratio in a hereditary disorder but am reminded of a similar age and sex incidence in the careful community surveys of Goldberger and associates on pellagra. The possibility that adult males might be eating more often away from home would suggest either a deficiency disease or more likely that some food substance, perhaps one that is relatively new to this population or one that becomes toxic in storage and which women and children are more likely to eat, could account for the reported age and sex distribution.

I am reminded of the circumstances on Guam and the manner in which the Chamorros have over several centuries learned to handle and consume safely local toxic food products such as cycad nuts (federico) and manioc (cassava). These are hardship foods and during the recent war years were used when other foods were in short supply. Some of the younger and inexperienced people were said to have been poisoned because they neglected to follow the old ritual of repeated washings and soakings which were required to remove the toxic glucosides from these foods. (See attached from Dr. Marjorie Grant Whiting.)

It would seem that a more careful delineation of the population affected with further information on age, social and economic class or caste, occupation, and particularly detailed reports on food and water supplies and food preparation and consumption would be helpful. To satisfy criteria for a genetic hypothesis careful pedigree, twin and consanguinity studies with the required parental identification from blood grouping and other measurements are required.

If Dr. Gajdusek would welcome the assistance which this Branch could offer (subject to approval by the Director), Dr. Marjorie Grant Whiting, a nutritionist from the Harvard School of Public Health, who is now cooperating in our amyotrophic lateral sclerosis (ALS) project among the Chamorros and Carolinians of Guam and Saipan, could be asked to assist him in New Guinea.

She is an authority on native foods and is particularly well acquainted with recognized toxins of the Pacific equatorial islands. (The circumstances related to ALS are quite different from those of Kuru, and although I seriously doubt that a good toxin plays a role in the etiology of ALS, I have encouraged Dr. Whiting to carry out her planned investigations.)

We could assign on a short-term basis, one of our Epidemic Intelligence Service officers to aid in the study of distribution and population selectivity.

Our geneticist, Dr. Ntinou Myrianthopoulos, would be available for consultation or direct services if desired.

The phenomenon among the Fore people, if properly evaluated and clarified, might be of value in some of the rare but devastating central nervous system disorders which are encountered in the United States. It would seem appropriate to offer to Dr. Gajdusek the benefit of our experience or the assistance of some of our personnel.

/s/

Leonard T. Kurland, M.D., Dr. P.H.
Chief, Epidemiology Branch
National Institute of Neurological
Diseases and Blindness

August 20, 1957

(From Marjorie Grant Whiting to Leonard T. Kurland - August, 1956)

Previous work on this subject: Cycas Nuts and Amyotrophic Lateral Sclerosis

(from application for Pre-Doctorate Fellowship submitted to
National Institutes of Health, July 1955.)

During my work on Guam, and subsequently during travel in Micronesia, P.I., Taiwan, Japan and Hong Kong, I gave particular attention to native foods reputed to have harmful properties and was struck with the toxic potentialities of cassava (Manihot utilissima) and federico, a starch made from the nuts of Cycas circinalis, the latter particularly.

I was impressed by the frequency with which Guamanians include federico among the possible causes of "creeping paralysis", a local name for the syndrome of amyotrophic lateral sclerosis. In food shortage periods, as during the Japanese occupation of World War II, this starch becomes a staple item in the native diet.

Since returning to the U.S., correspondence and library research provide sufficient evidence to justify further investigation and study of this lead--specifically, the possibility that nuts of Cycas circinalis may be an etiologic factor in amyotrophic lateral sclerosis.

Nuts from Cycas circinalia

This plant, growing wild in the jungles of many Pacific Islands, survives hurricane and drought and produces nuts the year round, which with careful preparation (soaking and cooking) can be made into starch used for soup and bread-stuffs.

A few Guamanians are never able to develop a tolerance for food made from this starch, and it is well known on the island that the wash liquid from the nuts will cause death to chickens if they drink it.

Besides this hearsay evidence suggesting that cycas nuts may possess harmful properties, a limited number of scientific studies tend to confirm their toxicity. In reports dating back to 1847, members of the same plant family (Cycadaceae) and of the same genus (Cycas) have been shown to be responsible for serious losses of cattle in Australia. Two distinct effects on animals, based on field observations and laboratory experiments are described. One is an acute gastro-enteritis frequently terminating in death; the other is a chronic neurological syndrome manifested by an irreversible and progressive paralysis in the hind legs of cattle, sheep and horses, which produces a peculiar gait referred to as "wobbles". In 1938, the Poison Plants Committee of Queensland confirmed earlier studies that Cycas media is toxic to bovines. Although Australian aborigines apparently could eat the nuts, after appropriate preparation, there are numerous reports of white men, for example Captain Cook's

crew, who suffered acute illness from eating them without first soaking the fresh nuts.

A possible rationale for soaking and cooking is implied by the discovery of a toxic glucoside from *Cycas circinalis* in 1903 and more recently in 1954 another toxic glucoside from *Cycas media*.

43c appendix

[COPY OF OFFICE MEMORANDUM]

To: M. Shy, Clinical Director, NINDB August 26, 1957
From: J.E. Smadel, Associate Director, NIH
Subject: Dr. Gajdusek's Paper

You will be interested in the accompanying letter from Dr. Garland.

Even before this arrived, I thought it might be desirable to add a paragraph describing the preliminary information on the pathology. Would it be feasible or desirable for Dr. Klatzo to prepare such a paragraph that might be added as an addendum to the manuscript under the usual introductory sentence, "The author is grateful to Dr. _____ of _____ who has provided the preliminary information on the microscopic pathological changes."

Joseph E. Smadel, M.D.

Enclosure

cc: Dr. Igor Klatzo

The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts
August 15, 1957

Dr. Joseph E. Smadel, Associate Director
National Institutes of Health
United States Public Health Service
Bethesda 14, Maryland

Dear Dr. Smadel:

Some of my associates and I are greatly impressed by Dr. Gajdusek's description of "kuru" and the picturesque background of his studies.

There was unexpected opposition to its acceptance at last week's editorial board meeting, however, on the basis of a lack of any proved morbid anatomy, pending the results of microscopic examinations--which will, apparently, go to another journal when they are available.

We have at present, therefore, a clinical description of a fatal disease of the nervous system occurring in a remote area of the world, with no positive pathological findings on which to base a definite diagnosis. I am personally eager to accept the paper, which describes the clinical features so admirably, but believe that the subject should be presented with caution, since authentically new diseases, I am told, are infrequent and difficult to come by. Much of the weight that such a paper will carry depends on the credibility of the evidence and the reliability of the author, and I think that we must depend on you for such assurances if the paper is accepted against the opposition that I have encountered.

I realize that you can't do much more than to repeat your previous statements, but I shall welcome any further information and also the photographs that you mentioned in your letter of August 6. If we decide to go ahead with the paper I shall use it as a special article and publish it as soon as is now practical--probably early in November.

Any further decisions will be made by Ted Ingalls, who will be in charge of the Journal for the next two months, during my absence. He agrees with me in regard to Dr. Gajdusek's paper and will see this letter before it goes to you.

Sincerely yours,

/s/

Joseph Garland, M.D.
Editor

JG:acp

43e appendix

(NIH)
August 29, 1957

Dear Ted:

This is concerned with the manuscript of Drs. Gajdusek and Zigas dealing with kuru which has been submitted to the New England Journal of Medicine. In particular, my letter replies to Dr. Garland's note of the 15th.

I quite agree with you and Dr. Garland that Gajdusek's paper would be much improved by some mention of the histopathological changes found in the brains of patients with KURU. Fortunately, since the manuscript was prepared in New Guinea, Gajdusek has sent to Bethesda the fixed brains from six cases. These are in the process of careful examination by Dr. Igor Klatzo of the National Institute of Neurological Diseases and Blindness. Dr. Klatzo and Dr. Milton Shy, the Clinical Director of NINDB, rightly hesitate at this time to provide a detailed description of the changes which are present. Nevertheless, the lesions which they have found are extensive and are common to all six cases. It is planned that Drs. Klatzo and Gajdusek will prepare a detailed report after the latter returns to this country. In the meantime, Dr. Shy and Dr. Klatzo suggest that the brief paragraph given below be added to Gajdusek's manuscript:

"The preliminary pathological study of six cases reveals a widespread neuronal degeneration. The cerebellum and extrapyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus, and pontine nuclei."

Drs. Shy and Klatzo are of the opinion that the above material should be used without direct reference to either of them. I would suggest that the paragraph be added as an addendum to the manuscript with a lead-in such as the following:

"ADDENDUM: Since the manuscript was submitted additional fatal cases have been autopsied. The preliminary pathological study (continue the above description).

Within the next ten days I shall send you six of Gajdusek's photographs dealing with KURU patients. I suspect that you may wish to use

several primarily to present the general idea of the disease, the patients, and the locale. Frankly, the still photographs do not provide the convincing evidence of severe neurological disturbance which is so clearly depicted in the several hundred feet of movie film which Gajdusek took of a number of the patients and which have been viewed by our neurological staff. Nevertheless, one or two of the stills would, I believe, add interest to the article.

Best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. Theodore H. Ingalls
Associate Editor
The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

CC: Dr. Garland
Dr. Gajdusek
Drs. Shy--Klatzo

JES:cte

(NIH)
September 12, 1957

AIR MAIL

Dear Carleton:

Dr. Bailey, Dr. Klatzo and I have just looked at your Kodachrome movie film which was taken at Moke and Kemi on August 7 and 8. The photography is excellent. The color is very fine except for one short sequence which was overexposed. Whatever the difficulty, it was promptly resolved by you.

One generalization which must be remembered by all who transfer from stills to movies is worth repeating--don't pan! It is almost impossible to swing a small movie camera for a panoramic view if it is held by hand. Furthermore, even with a tripod, the beginner almost invariably swings the camera too rapidly. This produces a jiggling effect when the film is projected and may produce seasickness in the audience. If you must have a panoramic view, use the tripod and rotate the head one quarter to one half as rapidly as you think it should be rotated. If you hold the camera in your hand, operate it for ten seconds, stop, move across one half a field, operate for another ten seconds, stop, etc.

Take all future movies at 24 per second!! It is almost impossible to transform 16 frame movies into 24 frame movies, and practically all good sound movies are taken at 24 frame film at a cost of about 16 cents per foot. However, such a product is not suitable for general use or for teaching; it is essentially limited to home use.

Yesterday I sent you a carbon copy of my letter to the editor of the New England Journal of Medicine. I am sure that you could have written more intelligent legends for the three photographs I sent the editor. However, only one of the four patients illustrated in the photographs has a clinical record here. Let's have the rest of the clinical records beginning with those of the fatal cases.

Dr. Klatzo showed colored slides illustrating the CNS lesions in the patients. The degenerative changes are really interesting. He will write you an informal note giving you a tentative description,

Everyone here continues to be greatly interested in the disease you uncovered. The leaf we received from you has been identified by Dr. Bernice Schubert, a botanist with the Department of Agriculture at Beltsville, as belonging to the family Araceae, genus Homalomena, species as yet undetermined. She was fortunate in being able to consult Dr. Jacques Barrau, a botanist with the South Pacific Commission who is an expert on plants of the New Guinea area. He states that the roots of the plant in this family are often used in native medicines in Malaya and Indonesia. It is interesting that alkaloids are not known to occur in this family.

Dr. Schubert asked if it would be possible to receive from you one or two complete plants in order that she may have a flowering spike and a fruit.

Dr. Evan Horning is interested in undertaking toxic studies on the plant which is reputed to cause tremors similar to those of KURU. He suggests that you obtain one and one-half to two pounds of dried leaves. In order to do this, approximately five to ten pounds of wet leaves should be collected. If the weather is dry enough, the leaves can be spread out and dried by sunlight after which they may be placed in the container for mailing. The customary way of drying the leaves is to place them on a screen six inches above 100-watt light bulbs. If the weather is too damp for drying the leaves in the sun, perhaps you can arrange some way to heat them; they should not be heated to a temperature which would scorch the leaves.

It may be helpful if a pound or two of the fruit of the plant could also be sent along with the whole plants referred to above. Send them back by air express converted to a government bill of lading. Special tags which will expedite the passage of the material through Plant Quarantine are enclosed for you to tie on the packages.

Best wishes.

Sincerely yours,

/s/ Joe

Joseph E. Smadel, M. D.
Associate Director

Dr. D. Carleton Gajdusek
Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea

Enclosures

P.S. Dr. Horning has also just requested one or two pounds of the rhizomes if it is possible to obtain them.

44a enclosure

September 11, 1957

AIR MAIL SPECIAL

Dear Ted:

I was glad to get Mrs. Papen's note and a copy of her letter to Dr. Gajdusek indicating that his paper on KURU had been accepted.

Enclosed are three photographs and accompanying legends which you may wish to consider for publication with the KURU paper.

I note in Mrs. Papen's letter that a set of galley proofs will be sent to me. I shall read these and return them promptly to you.

Best wishes.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Dr. Theodore Ingalls
The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

cc: Dr. Gajdusek

JES:smh

P.S. Thanks for suggesting a more descriptive title for Gajdusek's paper.

Legends for Figures to accompany Dr. Gajdusek's paper on KURU:

Figure 1 - Three Fore children with Kuru accompanied by their fathers. The disease was of several months' duration when the patients were photographed in March 1957. The children died in the ensuing four months.

Figure 2 - Aranaka, who is being supported by his father, had been ill for about two months when photographed in March 1957. This Fore boy died four months later.

Figure 3 - Group of Fore children assembled in their village for examination for Kuru. The Amanuensis sits in the foreground while a number of men of the tribe watch the proceedings.

44b appendix

Refer to: NBI:CP

(NIH)

September 13, 1957

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(At Okapa Patrol Post, via
Kainantu, New Guinea)

Dear Dr. Gajdusek:

I had the privilege to receive, through Dr. Smadel, 6 brains from the Kuru cases which you sent to the National Institutes of Health. My associate, Miss B. Garry, M.S., and I have been studying, during the past few months, the pathology of these cases. By now you must have received our preliminary findings on the first complete case (Yabaiotu) we have had the opportunity to examine. The incomplete survey of the remaining cases reveals that all of them show pathological changes within the CNS; however, the intensity of the process varies from case to case. The complete and thorough work-up of all the cases will undoubtedly take some time, since a great variety of techniques must be used, and topographically all the anatomical units within the CNS should be screened as completely as possible.

The brains generally arrived in a good state of preservation, except Natameia and Aranaka, but even these two brains are still usable for histological studies.

If I may express a suggestion, it might be better to fix the brains somewhat longer (3-4 weeks) at your center (brain immersed in 15% formalin, suspended by the basilar artery, corpus callosum cut) with possible exchanges of the formalin several times. The other thing I wanted to ask you is whether it would be possible to get more complete spinal cords and dorsal root ganglia (also a few more peripheral nerves) to have the pathological material completely covered.

We have received the clinical histories on four cases (Kinao - brain not available, Yabaiotu, Natameia and Yoeia) and we are anxious to have the histories on the remaining three cases (Inome, Mulinapa and Aranaka). This clinical information is very important to us for pathological investigation and for future publication of these cases.

I am afraid I am unable to give you any useful leads as far as the etiology of this disease is concerned. It seems to be definitely a new condition without anything similar described in the literature. The closest condition I can think of is that described by Jacob and Creutzfeldt. However, in cases reported the neuronal degeneration was most intense in the cerebral cortex, also no cases involving children or adolescents are mentioned. The etiology of Jacob, Creutzfeldt condition is entirely unknown (only about 20 cases have been reported). Since there are no known hereditary disorders resembling even remotely the Kuru condition, I am inclined to suspect some toxic metabolism responsible for the process.

We sincerely admire the splendid work you are performing despite the adverse conditions and we are looking forward to meeting you in Bethesda.

With best regards.

Sincerely yours,

/s/ Igor Klatzo

Igor Klatzo, M.D., Chief
Clinical Neuropathological Section
Surgical Neurology Branch
National Institute of Neurological
Diseases and Blindness

IK:ak

44c appendix

Jacques Barrau
Docteur Es-Sciences
Ingenieur I.A.T.

Washington 14 September 1957

Dear Dr. Gajdusek,

Being in Washington for a few weeks, I received thru the new crops research branch, U.S. Department of Agriculture, the botanical specimen you sent to N.I.H. The plant belongs to the family "Araceae", most probably to the philodendroideae, philodendreae. Without the inflorescence, it is rather difficult to tell you what is the species but I am sure it belongs to the genus HOMALOMENA.

Several plants of this genus are used in native medicine in India and Indonesia. The natives there said that it is a stimulant and a aphrodisiac. Moreover the plant has been reported to have an irritant action and is said to be used as dart poison.

Its use in New Guinea was not known. I should be very grateful if you could send me more information on the locality, where you found the plant to be used, the method of preparing the leaves, if any, and more details on the effects resulting of the consumption of the leaves. A complete specimen with flowers will be also extremely useful but I hope to be able to collect the plant myself as I plan to visit New Guinea once again during the next few years.

I am sorry to ask you so many questions but I am really interested in the ethnobotany of Melanesia and this Homalomena is something new in this field.

With many thanks in advance.

Yours sincerely,

/s/ Barrau

Jacques Barrau

C/o Plant introduction and collection section
South Pacific Commission
Noumea. New Caledonia

P.S./ I hope you will forgive my poor, basic English. I am French.

TELEGRAM

Dr. D.C.Gajdusek
c/o Dr. Zigas
Okapa Patrol Post
via Kainantu, Eastern Highlands

September 17, 1957

PHOTOS TEXT NEW ENG JOURNAL WERE ROLL 1 FRAME 12 AND 35 ROLL 6
FRAME 28 STOP YOU AIRMAIL JOURNAL YOUR CAPTIONS REQUESTING SUBSTI-
TUTION FOR MINE STOP ADD METAL FREE BRAIN TO SHIPMENT KURU BRAIN
MENTIONED YOUR CABLE STOP

Joseph E. Smadel
Bethesda, Maryland
via Washington, D.C.

Pintogōri, Okapa Patrol Post
via Kainanti, Eastern Highlands
Territory of Papua and New Guinea
September 18, 1957

Dear Joe,

I returned yesterday from a month of extensive walking and patrolling, some through country not previously visited, to hamlets and settlements first visited by Europeans, and on this patrol have completed some 1000 to 1500 miles of mountain climbing and walking, often with bush cutters to clear the trail, trying to track down kuru epidemiology since March 14th when our study started. To return to the extensive mail from NIH was a wonderful thing and I cannot thank you sufficiently for all the fine assistance that Dr. Carl Baker gave me while you were at the polio conference in Europe, for the supplies, the film etc. from the NINDB and, especially, for your own help in selecting the photos for the NEJM article, and adding the pathological report. Finally, the wonderful work of Dr. Henry Imus and Dr. Leonard Kurland is the first really sharp critical evaluation of our work we have received in such detail, and I am most grateful for it.

Dr. Kurland, of course, does not know that most of our time is and has been spent on epidemiology. Entomological surveys, extensive botanical and geological surveys, trace metal analyses of food, smoke, fire ashes, soil, etc. have all been arranged for and are still being carried out. For three months Lucy Hamilton, an expert on native diet and nutrition for the entire territory, has been in full time collaboration with us; she has prepared with us the extensive food lists of all the food, paints, native products, etc. which the Fore infants, children, men and women, the kuru victims and non-kuru victims, come in contact with. This work has been done for the hamlets and houses with current active kuru and contrasted with similar situations and populaces without kuru. The Fore, all of whom are in the "kuru region" have been compared in this respect with surrounding non-kuru populaces, and those linguistic groups with kuru in one part (i.e. adjacent to the Fore) are being compared to those portions of the same groups without kuru. Botanical, zoological, entomological taxonomy on all species eaten, involved in occasional pica, chewed for salt, used in fires, used in sleeping houses (the smoke) and used in cooking, are all being done. Thus far, we cannot find a single clue.

Three months of intensive work by Lucy, seven months by myself, and the added linguistic-anthropologic help by Dr. Smythe, who is an expert on Melanesian Languages, has netted us not a single clue as to what might be "poisoning" the Fore--not a single sign of a dietary deficiency. Experimental approaches, such as removing patients from all contact with native products, as far as possible, for months--with continued progression of their illness--have been tried. Epidemiological case plotting, past and present, has shown cases who develop into severe and fatal kuru after a complete exodus from the kuru region, and other cases apparently starting

in kuru-free regions after marriage into such regions from kuru populaces. However, an increased number of "recoveries" at these borders...all still fit the hysterical hypothesis...rare, but semi-documented cases from low kuru incidence regions, getting kuru in the kuru region...none from absolutely kuru-free populaces have yet been found with a case of kuru on residence in the kuru region. Studies of all toxic, possible toxic, and medicinal herbs, minerals, and plants is underway. But, without a trace of increased or special exposure in either the kuru patients as opposed to normal Fore, and, in addition, without a trace thus far detected of the real differences in food habits or environmental exposure between kuru populaces and kuru-free populaces, we are thus far totally stalled on the toxic approach.

Case plotting geographically, chronologically within a small set of hamlets (tribe or clan) as to ground, gardens used, living and sleeping houses, eating patterns, etc., all fail to show any accumulation of cases or simultaneous cases. Familial incidence is conspicuous and high, but as a rule, siblings and mother tend to be sick at widely different times, often with illness years apart and often with place of onset miles apart--different years. Thus, Joe, all of our work is designed to prove current or antecedent infection or to demonstrate a current or a past toxic exposure, via skin or any body orifice. Nothing yields a clue to us thus far. Two cases in a single village occur in distant, remote hamlets of the same village, in two individuals coming into contact rarely. When the disease strikes the same "family" or household again, it is living at a different site; often different preparers, etc. are involved, and it is often years after the death of the first in the family. A few exceptions, with parent and sibling having the disease within a few years of one another, and a rare, simultaneous case (one instance) have yielded no added information on careful study thus far.

Thus, we are well aware of the unlikelihood of such a phenomenon with such astounding, unprecedented incidence being genetic--but what can we do? I am constantly playing with the hypothesis of antecedent infection, perhaps a mild encephalitis, giving rise to a post-infectious process. Even our AICF test has been used on the cases without help, but we cannot yet find a suitable clinical entity via case study, anamnesis, nor by study of all illness in the region for over half a year now. I am naturally most anxious to have further neuropathological reports. Your preliminary reports are so impressive, so contrary to preliminary reports on one brain from Melbourne, and a further two have not yet been reported, that we are astounded--yet, of course, much encouraged.

We at least have something in the neuropathology to anchor on.....and our ward full of dying cases at the moment demonstrates to us every moment that there must be CNS pathology visible....there is far too much evidence of extensive neuropathological lesion clinically. In recent months we have proved to ourselves that the lesion has to be diffuse and that cerebellum and basal ganglia in addition must be involved. This now is clearly evident from examination of our patients and at the moment, with a film team from the government finally here, I am trying to show this clearly in cine film. This you will shortly see and together with the longitudinal studies of single cases which our early cine effort have made possible, there should be no problem demonstrating most of the clinical features, and some of the epidemiological features, of kuru to research audiences of potential collaborators. The film is designed not for instruction, but for consultation with research associates to get added advice and opinions ----just such as Dr. Kurland has supplied.

We have now tried stilbestrol,, testosterone, cortisone further without help. BAL proved of little or no value in repeated courses. Tranquilizers are en route and will be tried further. Strep studies on the nasopharynx of patients and extensive blood group genetic survey of kuru patients and all kuru involved and surrounding kuru-free populaces are well underway.

I am sending today two more fixed brains from children with classical kuru. They have stood for over 1 month in fixative. Also, fixed tissues on these patients, including cervical cord, pituitary, adrenals, kidney, liver, lungs, heart, muscle, fascia, etc., etc. We have now plastic and glass containers on hand; we also have specially prepared trace-metal free formol-saline made at Hall Institute for us, using analytical re-agent NaCl and trace metal free HCHO and water. One such brain I shall send to Melbourne. Another such---along with other tissues similarly collected---I hope to send to you. When the trace-metal free brain arrives packed in plastic bag, please make certain that it does not get shoved into routine neurohistological channels, but rather gets appropriately handled for trace metal studies. All previous specimens have been fixed in usual autopsy room HCHO, the provenance of which I do not know, and kept in metal tins. Only this specially handled specimen will be really adequate for trace-metal studies and we hope you will be able to get the lot on it.

In a week we shall be off on the final Kukukuku patrol and then I shall plan to close down our field program and start homeward. A conference first in Port Moresby, a line-up of followup work....there will not be anyone in the field to collect further specimens, etc. once we close down, nor to assemble cases, track them down, etc. However, I am arranging all so that in 12-18 months a follow-up epidemiology could be done quickly and with profit, based upon our extensive current epidemiological files.

Will you let me know whether you selected any photos for the Australian Journal and sent any in to them, or whether you have sent them only to the NEJM. I telegraphed to you today asking for frame edge-numbers

from the negative on whatever pictures you selected along with negative numbers. Since I have a record also, I can easily write captions and rush them to the journal. If you have done so yourself, OK. If proofs are ready and mailed before mid-October I should get them in time for editing and prompt return. Mail is only 10-14 days, usually, in reaching here. Sometimes even faster....If I am around and not in the bush...and then I should be on hand. Finally, an additional review of kuru ---far more extensive than the previous and more "up-to-date" is off to you along with the next air shipment via Qantas. It is a rather lengthy manuscript which all who are following kuru should read...but which is, obviously, already a full month and one half out of date...and it replaces all earlier summaries. With it I am sending a stack of carbon copies of case records of deceased patients....some of whose names will be recognized from the pathological material in your hands.

All items summarized as sent to me or received from me in Dr. Carl Baker's letter of July 26th are correct.

We are working on and have been continually seeking a toxic factor. No one will appreciate having to study toxicologically the 500-odd food-stuffs eaten by our ForeKuru patients...as well as all other natives hereabout and thus far we can find nothing peculiar to either kuru, patients, kuru-affected populaces, households with currently active , or the age and sex group predominantly suffering from kuru. Without such a "lead" we are faced with the impossible task of toxicologically surveying some 500 species and varieties of animal and vegetable life of which the Fore partake. All will soon be taxonomically identified, and a search through our lists and commentaries by competent Pacific-Island toxicologists may be of help---and by botanical pharmacologists. However, who has seen anything like kuru following any known toxin thus far? Manganese poisoning, perhaps....but we cannot anchor on heavy metals as yet either from laboratory study of tissues or from local epidemiological study.

The first two 35mm still films have been printed up and prints have arrived here. From them I shall select photos for the Australian journal.. taking care that none used in the NEJM are duplicated in this second article. Thus I have requested number designations of those you sent to NEJM. I am having a map, a line-map which is rather simple and documents the kuru region, rushed from Melbourne to the NEJM for the kuru paper. If this gets there in time it also will add to the paper. If not, well and good. In any event, I am writing to the journal begging them to send you and to me also, here in NG, copies of the proofs. I shall, if possible, get them back in time.

The new shipment of tissues which is now off to you will have with it, insulated in plastic in case of fluid leakage, a stack of case reports--mentioned above--and the third kuru review (which has the more recent data and which, we hope, will provide a chance for publishing a definitive detailed regional epidemiological map and plenty of pictures. This is all we shall write....although I have material on some 50 children for a review of kuru in childhood, and data on everything from Fore genetic blood group studies to clinical lab studies and treatment trials on kuru to work up later, back in the U.S., for further reports. Obviously all

is of minor importance as long as etiology remains a mystery. As with EHF, we are thus far licked. Worse than with EHF, I can find no toe hold from which to start infectious disease or toxicological study. Further neuropathology may be the key matter, and obviously we are looking forward to further reports. How possible do your NINDB men consider a mild, usually clinically inapparent or minor, undiagnosible antecedent acute infectious disease from the neuropathological picture?

As far as deficiency: Fore diet is excellent, patients are well nourished, showing no sign of any dietary deficiency of any sort and occasionally even fat and strikingly well developed and nourished at the onset and well into their disease. Dietary supplement does not influence their course nor do vitamins in moderate dosage. Outsiders can spot only a superfluity of foods of every sort here in contrast to much of the rest of the Highlands. Water sources give us no clue.

Enclosed is a carbon copy of a few letters written back to our "base" during our last patrol, of most minor importance but perhaps of interest to anyone following kuru blow by blow.

My greetings and intense gratitude to Dr. Klatzo and Dr. Milton Shy for their help and collaboration.

Please let me know whether or not you will be in Bangkok for I shall be passing through at just about the right time for the meetings, as things are turning out.

Greetings to Betsy and all others in Washington who may remember me.

Sincerely,

/s/ Carleton

D.C. Gajdusek

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 19, 1957

Dr. Joseph E. Smadel, Associate Director
National Institutes of Health
Bethesda, Maryland
U.S.A.

Dear Joe,

Enclosed are two sheets, self-explanatory. However, they entail further work from the NIH in our behalf and I hope that interest there in kuru will be sufficient to warrant it. We are most grateful to you and everyone at NIH for all that has been done. The first set and the second set of photographic prints has arrived. From them we have selected a series of 12 for reproduction in the Australian article on kuru, which is longer than that appearing in the NEJM, written a month later, and which is based upon considerably more cases but differs in no very essential way from the "first report" in the NEJM. We are obliged to present the story in Australian medical literature and the Journal has already agreed to extensive illustration.

The enclosed legends will serve to document the 12 photographs we have selected. The prints we have sent to Australia are not properly retouched and many are not properly enlarged. Thus, we request that you ask your photographic department to prepare retouched enlargements...only one retouched copy of each suitable for publication and fairly large reproduction-- of these twelve photos and send them RUSH, Air Mail to the Journal's editor. The address is on the letterhead of the enclosed letter.

The following table will make possible identification of the negatives and frames:

<u>Designation used for the AUSTRALIAN JOURNAL</u>	<u>Negative Number in Kuru file</u>	<u>Frame number in Kuru file (or description)</u>
A	1	16
B	1	23
C	VIII (8)	34, 35, 36, 37 (enlarge all 4 and retouch the best for publication)
D	VII (7)	1
E	V (5)	32

<u>Designation used for the AUSTRALIAN JOURNAL</u>	<u>Negative Number in Kuru file</u>	<u>Frame number in Kuru file (or description)</u>
F	2	There are three successive frames of a woman sitting whose head is being firmly held by a native nurse--the nurse's white dress showing. The intermediate distance photo (not closest nor furthest) is chosen. This shows the strabismus best.
G	1	12
H	VII (7)	33
I	1	35
J	2	There are two pictures of a mother holding a child with decubitus ulcerations and head thrown back in her arms. Mother standing. The closer of the two is chosen.
K	1	21
L	2	The same child as in "J" but this time lying on a white sheet. Of the three such frames select the one showing a three-quarters view of face rather than a full view. The head is turned to patient's left. In the others it is turned to patient's right. Use picture with head turned to patient's <u>left</u> .

Thus, all but three can be specifically designated by numbers of frames on film edge and negative numbers. Film "2" two prints, however, were sent to me without numbers. Thus I must describe them. I think, however, the three descriptions are adequate.

The sheet of legends which I sent to the journal may be of help to you in interpreting the other photos, Joe, for many are other views of the same subjects which I have fully described in these legends.

We have now shot the entire 12 rolls of film which we got from you and from the NINDB and all are off in the mails to you. There is a further mass of Kuru material still unphotographed, many features of the disease still to be filmed, and much more we could do if we had more film. Thus, if the NINDB can see its way clear, we would welcome a further supply of film. Kodachrome is preferable to Triple X, for here in New Guinea the very bright light makes it difficult to stop down sufficiently for the ultra-high-speed triple X film. If you and others think we have done well on the first rolls of kuru 16 mm film you have seen, we can promise you much better and even more careful documentation should you give us more film. Finally, we can secure late follow-ups on patients now dying who have been previously followed in earlier stages of the illness. For final preparation of a kuru film, such horizontal studies are invaluable.

In an immense second letter I am sending you a manuscript of a more up to date review of kuru, newer statistics, further epidemiology, etc. This should arrive along with the enclosed letter, but I do not want to confuse this immediately important photographic request with the mass of other things discussed in the voluminous other letter. I hope there is someone at NIH or NINDB who can plow through all I have sent, for I believe it has value.

Sincerely,

D.C. Gajdusek

KURU RESEARCH FILM FILE

FILMS from PURARI-SUBU patrol from Highlands to Papuan Coast

Film No.

- | | |
|-----|--|
| P-1 | Moraei-Watcherapinti Kukukukus
Kukukuku baby with hare lip suckling |
| P-2 | Southern Moraei Kukukukus
Kuatnagunga - Monori |
| P-3 | Weme - village or YAR "Pawaians"
Sago Processing |
| P-4 | Weme - Sago Processing |
| P-5 | Weme - Sago Processing |
| P-6 | Weme - Sago Processing
Weme-Subu River junction |
| P-7 | Weme - census
Down Subu (Lamari) in canoes |
| P-8 | Down Upper Purari to Wa'abowa in canoes |

These films deal not specifically with Kuru patients, but with the anthropology of the Kuru-region and the surrounding non-Kuru region and many of the shots may be of eventual value in Kuru epidemiological work and study. Thus, there is no need to make very great enlargements of them, but in order to have them available for study, a single postcard size glossy print of each frame should be made, and these small enlargements, appropriately labeled with negative film number, filed away in the kuru file of black and white pictures, pending my return.

Please keep the negatives together, and do not mix negative strips. Exact identification of subject matter depends upon this keeping of the negatives intact and not mixing strips from one negative with those from another.

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 19, 1957

R. M. Winton
Editor
The Medical Journal of Australia
Australasian Medical Publishing Company, Ltd.
The Printing House
Seamer Street, Glebe
Sydney, N.S.W.

Dear Sir:

Enclosed you will find the signed assignment of copyright form which you requested we sign and return to your office. Enclosed we are also forwarding to you a set of photographs for illustration of the article. The map which is Figure 1 of the paper was already supplied to you with the manuscript and your office indicated that it was satisfactory. You suggested that we keep the number of photographs down to about 8. We are, however, submitting a total of 12 in the hope that you will publish at least the first 7 (lettered A through G inclusively) and one of the remaining 5 (which include photographs of children with the disease and are designated H through L inclusively). However, we believe they all contribute significantly to presenting the picture of this "new disease" and urge that you include as many of the last 5 pictures (lettered H, I, J, K and L) as you can.

The prints being supplied are the only ones we have on hand. They are not all appropriately enlarged and none are retouched to remove the blemishes inherent in the use of small negatives. We are writing now to the National Institutes of Health, Bethesda, Maryland, USA where our negatives are filed and where our photographic work is being done, requesting that appropriate glossy print enlargements with adequate retouching for publication be made of all 12 of these photographs and forwarded directly to your office. Upon receipt of these finished, retouched, glossy prints, you may proceed with publication of the article. The accompanying sheet provides captions for each of the photographs. You may number them and arrange them as you see fit.

Four separate photographs all labeled "C" have been supplied to you. All four are of the same group of 8 Kuru patients. Obviously, only one of these is to be used. We are leaving the selection of which of the four is to be used to the photographic department of the National Institutes of Health where such selection will be made upon the basis of which of the four enlarges and retouches to a better finished print for publication.

When you receive the retouched, enlarged prints of these 12 photographs from the USA will you please return to us the prints we are sending you herewith?

We know that photographic illustration is expensive, but believe that this disease, now being described for the first time, warrants full and inclusive documentation. It is a new disease occurring exclusively in Australian Trust Territory, and we believe that a full photographic coverage of it will add considerably to the quality of this report of kuru in your Journal.

Please inform us of the receipt of this letter and, again, at a later date, of the receipt of the finished glossy prints for publication from America.... for we are somewhat isolated and such notification assures us that there has been no loss of mail.

Sincerely yours,

D. Carleton Gajdusek, M.D.

ILLUSTRATIONS for article by Zigas and Gajdusek on KURU:

(illustrations are lettered in upper right hand corner of reverse side).

- A. View of part of Kuru region from the Kuru Research Center at the Okapa Patrol Post (elevation 6,500 feet), looking west toward Mt. Michael (elevation 12,500 feet). Mt. Michael is visible on the horizon on the right of the picture. Note the scattered areas of forest and of kunai grass covered slopes. Fore and Keiagana populaces afflicted with Kuru live in many scattered hamlets hidden in the forests and kunai of this picture.
- B. View of the Kuru Research Center and Hospital at the Okapa Patrol Post (elevation 6,500 feet).
- C. A group of six Kuru patients from the Fore village of Pa'iti in the southern part of the Kuru region. All are females and only one is a child. These 6 cases were present in a populace of only 190. Photograph taken in June 1957. By September four of these 6 patients, including the child, had died of the disease.
- D. A female victim of Kuru who has been dragged out of the native house to which she was already confined. Her husband and his second wife help support her. The others in the picture are all children of the patient. This patient died within one month after this photograph was taken.
- E. A middle-aged Kuru victim arriving at the Kuru Hospital on stretcher. This patient already had severe dysarthria, marked aggressive emotionalism, and she died only one month after this picture was taken.
- F. A young adult female Kuru victim showing the strabismus common in advanced stages of this disease. Two months later this patient died of her illness.
- G. A group of three Fore girls, all victims of Kuru and each sitting beside her father. All three patients died within three months from the time this picture was taken.
- H. An early pubertal boy suffering from advanced Kuru who shows marked strabismus.
- I. A prepubertal boy suffering from advanced Kuru who survived for four months longer. He demonstrated at the time the picture was taken a moderate strabismus and could no longer maintain a sitting posture without support.
- J. A more advanced case of Kuru than in figure I, in a girl of about 6 or 7 years of age who had lost her speech and had developed severe decubitus ulcerations. She died a few weeks after this photograph was taken.

- K. The same patient as in figure J two months earlier. An internal strabismus had already developed and advanced dysarthria was present.
- L. The same patient as in figure K two months later and only a few weeks before her death. Her mother restrains her left hand to prevent the choreiform involuntary movements which occurred every few seconds and interfered with photography.

NOTE: Four photographs have been lettered "C". All show the same group. Only one, of course, is to be used --which will depend upon which of the four is superior in quality when enlarged and retouched. All 13 photographs will be supplied in enlarged and retouched prints (glossy) from the National Institutes of Health, Bethesda, Maryland, directly to your office as soon as the photographic work can be handled.

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 19, 1957

Dr. Theodore Ingalls
Associate Editor
New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

Dear Dr. Ingalls:

Enclosed is a letter, - a carbon copy thereof, addressed to you but which I have just posted to Melbourne to be reposted to you along with the map discussed in the letter when the map is prepared. There will not be much delay. However, today I have had telegraphic advice of what photos Dr. Smadel has selected for our kuru paper and I hastened to send you here - with appropriate captions.

Film 1 Edge Number 12:

Three Fore girls, all victims of kuru, with their fathers. All three patients died within three months from the time this picture was taken and the brains of all three have revealed the characteristic neuropathological lesions of Kuru.

Film 1 Edge Number 35

A prepubertal Fore boy suffering from advanced kuru. At the time this picture was taken he demonstrated such dysarthria that he could no longer communicate, he could no longer maintain a sitting posture without support, and a moderate strabismus had developed.

Film 6 Edge Number 28 (this must be improperly designated by Dr. Smadel for it does not deal with kuru. I suspect it is Film 4 Edge Number 28, instead). If so, the accompanying legend will be used. It should be a picture of a Kuru patient, a middle-aged woman with obvious advanced pregnancy and with a protruding umbilical hernia, who is standing holding firmly to a stick for support. Her husband stands beside her, holding what I believe are a stack of cards in his hand.

Legend: A middle-aged Fore woman, a victim of moderately advanced Kuru, who stands clinging firmly to a stick for support. She could still walk, although on a broad, unsteady base, using the stick for support. She is in the last trimester of pregnancy and since this picture was taken has delivered a normal male infant who is thriving well in spite of his mother's advancing Kuru.

I trust that these legends will appropriately describe the pictures that you are using in the article. The selection is well made. If it appears that my descriptions do not apply to the films supplied (i.e. there has been some error in numbering), please inform me thereof by air mail. I can make final corrections in the galley proofs which should be mailed to this address as well as to Dr. Smadel. Finally, the minor corrections and additions listed in the enclosed letter, which you will receive again later with the map, can now be entered into the manuscript.

Sincerely yours,

D. Carleton Gajdusek, M.D.

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 21, 1957

Dear Joe,

Just after a stack of letters each of which had to be packed into a real package rather than an envelope, you no doubt would like a rest rather than more mail. However, now that a great shipment of tissues (including three brains) is off to you I will discuss herein a few remaining things of Kuru interest before packing up for another long patrol....the long-postponed Kukukuku patrol. In the pack of pathological materials is one trace-metal-free brain packed in plastic which has never even come in contact with the cotton protecting it and has been only in trace metal free formol saline in plastic containers since removed. This should be used for pathology and for all trace metal studies. It is from TASIKO, a girl of c. 6 who failed to respond to BAL therapy. Crude liver extract and BAL were the only treatment she received. Dozens of case records are in the paper-pack enclosed with the shipment.

We have just finished today shooting 3000 feet of 35 mm cine film on Kuru with the Commonwealth government's professional cine team. We had waited for them for months and months and went ahead with our own filming, as you know. However, they finally arrived, I assembled two dozen Kuru patients, and planned a rather extensive clinical survey of Kuru which we shot in 4 days. It lacks any chance of showing progression of the disease in single patients and also shows nothing of Kuru in its native village setting, since all was filmed here at our Research Center. However, it will be a professional rendering of the clinical features...and we tried hard to show many of them. I shall eventually get a 16 mm copy of the entire film off to you. It is made for advice from research collaborators and not as a teaching-demonstrating film. We hope that you will see things we did not know were in the film. However, this 3000 feet of film (actually 3200) will make 30 minutes showing. It is shot at 24 frames per sec. and copies are taken from a 35 mm master film. It is black and white. This material can be coupled with the 16 mm 24 frame/sec. material we have shot with the camera you supplied and which we shall continue to shoot. We shall concentrate on kuru in the native setting and on serial horizontal studies of individual patients....at various phases of their disease. Thus, the 16 mm material we shoot, amateur though it may be, can, we hope, be coupled with this professional material to make one rather exhaustive and comprehensive film covering everything from ecology, native setting, social setting, the research project, and especially, the clinical features of kuru. Other congenital disorders,

differential diagnosis with the contrasting congenital tremor, and such things as effects of cortisone, stilbestrol and testosterone therapy can all be demonstrated as well. Thus, this 3200 feet of 35 mm film taken will be a great addition to kuru documentation. This, together with the 16 mm stuff we have shot and hope to continue with, will give, I hope, a rather complete picture. Please let us know if the 16 mm film we have taken is useable and adequate. I have asked for more film in my last letters to you. Any that arrives will be used with caution and care. It can never be wasted documenting late and terminal stages of the disease in patients studied on film in the earlier stages a few months ago.

After the Kukukuku patrol we shall have a Kuru conference in Port Moresby. Actually, field research has been restricted to Vin and myself and to our nutritionist Miss Lucy Hamilton. Dr. Smythe was with us for a month working on grammar and his grammatical analysis of Fore--preliminary--has just arrived and is of much help in our work. However, fully half the time Kimi, Keiagana, Usurufa, Kanite and other languages are the problem. Our last patrol revealed that Kuru involves all of the small and narrow belt inhabited by the Kanite peoples rather than part of it, and the same applies to the Usurufa tribal groups. These people are thus entirely involved in Kuru...not only partly, as we had thought.

However, since they number under 1000 total (each group) and live only in a narrow belt all of which "borders on the Fore" and since they all marry into Fore this does not alter our thinking any. Late.... a cultural group closely related to Kanite and Keiagana....is also involved in Kuru, we find. Thus the Kuru region is a slight bit larger than we had thought, but we have established fully the extremes of its borders. Only one case has yet been found outside of these "limits of the Kuru region". That is a case in a woman who developed her disease while visiting her home in the Kuru region but who walked to Lufa with her husband-- an arduous 4 days of mountain climbing-- in very early illness and died at Lufa after 3 months or so slow progression of her illness in this densely populated but Kuru-free region. She thus demonstrates that very early Kuru can run a full course to incapacitation and death in a totally Kuru-free region in a cultural group devoid of Kuru. This woman was brought in by marriage as only three Kuru-region women have been to this group. The other two are living and well. Moreover, she lived for over a year in the Kuru-free region of Lufa, west of Mount Michael, with her husband after leaving her home and noted Kuru first after a return visit to her Kuru region home, after only a week or two back in kuru region. Such cases make it most

difficult to think of infection or toxin....yet, Joe, that is what we are thinking of and concentrating on but, unfortunately, with no leads. I am asking Lucy Hamilton to prepare a collection of those plants and native products which for some reason or other we have wondered about, suspected or been disturbed about. These will go off to you for taxonomic and toxicological analysis of whatever sort the Smithsonian and others at NIH can get for us. The full taxonomy of Fore diet is being done but we have no expert on toxic plants, etc.

Sincerely,

/s/ Carleton

Contents of Shipment of Kuru-pathological specimens to National Institutes
of Health for Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland
U.S.A.

Three fixed brains from Kuru patients.

1. Brain from ASO F-13 yrs.
fixed and hardened in 5% formol-saline
2. Brain from IAMOGI F-16
fixed and hardened in 5% formol-saline
3. Brain from TASIKO F-7
fixed and hardened in 5% formol-saline specially prepared
with chemically pure HCHO in analytical reagent NaCL.

This brain was promptly transferred on removal to a plastic container---trace-metal-free---and after hardening it has been wrapped in one of the plastic bags you people supplied with the camera (the best we could find). Cotton has been placed around it....But No Direct Contact with the brain...and the brain completely protected by plastic from contact with anything else. THIS IS A VERY SPECIAL SPECIMEN which should be used for both neuropathology and for all special trace-metal studies, etc.

Fixed tissues from ASO, IAMOGI and TASIKO in 70% ethanol...third change...after 24 hours fixation (ASO and IAMOGI, slightly longer) in freshly prepared Zenkers' acetic acid. These are in 3 specially labeled bottles.

Fixed tissues from TASIKO...in trace-metal free formal-saline. These were placed in a bottle, not specially cleaned, but rinsed repeatedly with our trace-metal free formol-saline before filling and putting in the tissues. They have remained in the original trace-metal free formol-saline. These pieces of all viscera, endocrine glands, etc. include pituitary, cervical cord, etc. Do not lose small pieces when removing for pathology.

Cerebrospinal fluid on four Kuru patients for trace metal studies.

A small pack of slides of blood films from Kuru patients taken at various phases of illness. Perhaps some hematologist would care to look at these old, none-too-good, films. A few unstained films are also sent. All from Kuru.

A package of papers pertaining to Kuru, essentially the carbon copies of case records on deceased patients. These include full clinical records on all of those patients on whom you have already received pathological specimens. The pathologists may be interested in seeing them. Please keep them all in the Kuru File. (There are two recent reprints of mine in this pack, for Dr. Smadel).

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 27, 1957

Dear Joe,

We leave for the Kukukuku patrol and an attempt---one of the few made---to "cross the island" i.e. we hope to track down populations south of the Fore back down to the Yar people with whom I previously made contact and thence on down the Purari River to the Papuan coast. It is fully "unexplored" and we cannot guess yet how we shall succeed.

Enclosed is a list of the "contents" of the last, i.e. the 12th cine film sent to you and also a list of the additional four 35 mm black and white still films for post card size printing for the Kuru file. These are undeveloped films not in cassetts and thus please warn whoever receives it not to open the film boxes until in a dark room, for if they do so they will ruin the films. The last cine film has more "background" material than Kuru...but it is important background stuff. With 3400 feet of professional 35 mm film being shot on Kuru clinically....a good 16 mm print of all of which I shall eventually get off to you once I edit it in Port Moresby....we thought we could use a roll or two on epidemiological and ethnological background material which the 35 mm professional film will have none of. Since all the 35 mm was shot here at Moke (Okapa) on a few days using a group of 2 dozen patients I collected for the purpose, it has no background ethnology, no epidemiologically or ecologically significant shots and, what is most serious, it cannot show the progression of the illness in a single patient. It is by following up patients whom we have previously photographed that we can get this "horizontal" documentation which we are now after...thus I hope more film will be forthcoming. I went and used my own funds to buy a few more reels of cine Kodachrome which I shall shoot on the Kukukuku- Papuan trip and send back to you. It is Australian Kodak with full developing charges prepaid...which is no longer permitted in the U.S. Thus, it should be developed for you in the US without charging for the developing. Please pass this word on to whomever handles the film....for Kodak anywhere in the world is supposed to recognize this prepayment of developing charges which they have already collected here in Australia-New Guinea.

In addition I am sending sundry other carbon copies for the Kuru file. Among them is some identification of spiders eaten mostly by women and children (the usual Kuru victims).

Lucy Hamilton will be collecting the medicinal plants and drugs of the Fore and also all the plants, varieties and species of food-plants which we have reason to suspect. These she will send off to

you while I am on patrol. Things eaten, especially by women and children (usually kuru patients), and items which our kuru patients seem to have eaten more regularly than other people, as well as items we have reason to suspect in their being peculiar to the kuru region or, at least, changing in variety throughout the highlands from region to region will all be sent for:

- 1) botanical (zoological, in the case of food, insects and animals) identification;
- 2) comments by whoever is qualified on the likelihood of toxic alkaloid or other toxic products being a species variety of the genus involved;
- 3) comments on any known pharmacological or toxicological properties of the specimen or related specimens; and,
- 4) suggestions as to which might be advisable to pursue more intensively by physiological and toxicological and local ethnological food habits study.

In addition, Lucy will get off to you, via the Bureau of Plant Introduction, a shipment of the kuru-like-tremor-producing plant, as requested. It is all hearsay, for we have not seen it used. However, all informants agree on the information. We shall try to get a complete Fore ethnobotanical file off to you. A crew of entomologists are soon to be with us for a week or so trying to identify all food insects, of which women and children particularly eat in large numbers. However, I suspect that Smithsonian sources will be of more help eventually than our visitors. They will be asked to make a survey of ectoparasites in dwellings of kuru patients, and to comb rodents living in the dwelling thatch for fleas, etc. Furthermore, I hope to ask for an intensive search for all biting insects about the houses, gardens and haunts of the kuru patients, to get some idea if we have missed rare mosquitoes--they are known to us at this altitude--and to get information as to what species of fleas, ticks, sand flies, etc. bite in this region.

I have given Lucy the addresses to which to send the specimens: formaldehyde-pickled things, directly to you at NIH; unpickled botanical specimens via the Department of Agriculture, Office of Plant Introduction, from the address cards which you sent me.

I have received word of the pathology from Dr. Klatzo and am most excited and anxious to learn if further work bears out these results. Three well fixed brains are off to you. I have managed to keep four terminal patients around this month, and we may (?) be able to get the brains on some of them, at least. It is most difficult and most terminal patients

must, on the insistence of villagers and kinsmen, be returned to their home ground for their death and burial. Thus, we miss most possible posts and those we get are a difficult politic.

Last week, one of our friends from Aga came in to report that his clansman had eaten his grandfather, against his advice. Such recent, nay current, episodes of cannibalism are not unusual here, but it is highly unlikely that all of our kuru patients have eaten human brain or ectoderm and, thereby, gained human neuroectodermal sensitivity...a remarkable concept which Anderson discussed with me many months ago. It is so unique a concept, and such a romantic one, that I almost wish cannibalism was more prevalent than it is. Ritual payback murders, usually for kuru sorcery, are a regular occurrence, and the tribesmen do not like to be interfered with in their vendettas. A gang are now in the kalaboose for "putting bows" in the police from our post, who went to investigate the last murder. A day's walk from our Research Center, the upper Lamari people held down a patrol with arrow fire for some time last month. We now head for restless areas and are proceeding with due caution. But thus far, all this sounds far more "dangerous" than it has been, for our Fore, Kimi, Keiagana, Usurufa, and Kanite friends and patients have been friendly, helpful and cooperative, and except for "trusiworthy" seem to live up to the Boy Scout's oath, rather well. I shall write to you from patrol.

Sincerely,

/s/ Carleton

Carleton

P.S. Lucy has found a few additional plants reputed to produce "tremors", and these we shall also collect for identification. However, the plant you have already received is exclusively a Fore drug, making it more interesting. We cannot pin the use of it, however, on our kuru patients, and we cannot yet verify the rumor as anything more than legend...we have not actually seen it consumed.

One cine film (16 mm) and two undeveloped black and white negatives sent:
Cine Film No. 12 --- Kodachrome. shot at 24 frames/sec. No filter.

Date:

8 September 1957

Mani...central Kimi...rest house area during medical inspection of one of Mani census lines. John Berkin, European Medical Assistant inspects line along with our Fore boys who work as orderlies. Patients coming to medical boxes for treatment.

23 September 1957

Day-time sing sing and pre-mumu dance at Henegaru of Taramo region in Keiagana cultural and linguistic group. Traditional "clowns" appear in the dance.

35 mm still films sent for developing of negative and for post-card size prints of each frame (glossy) to be made for Kuru film file and stored in NIH pending my return. Do not send prints back to me, just make post-card size print of each frame, number each appropriately so that they can be identified, and file for eventual classification by me on return.

35 mm STILL films Nos. 9 and 10

The subjects of these films I cannot list, but when I see them, if they are kept in proper sequence....I can identify everything.

Second shipment containing only Two 35 mm black and white negatives, both undeveloped, both Plus-X film, and both not in cassettes....thus it is imperative that films be unwrapped in dark room!!!!

These two black and white films are still films Nos. 11. and 12 of Kuru-film file. Post card size glossy prints should be made of each frame and the stack of films, identified by negative number, filed with the Kuru film file for eventual identification by me.

Film 11:

Photographs all taken on 25 September 1957 at Moke-Pintogori Kuru-Research Center.

The entire film consists of many, repeated, serial shots of only three Kuru patients in Kuru Study. All are taken within a few seconds of each other in an attempt to show facial expression, strabismus, sl. ptosis, and other features of advanced Kuru in children.

Patients, in order of appearance:

ATONA...advanced, near-terminal Kuru who has had repeated BAL therapy courses as well as high-dosage Crude Liver Extract therapy.

ISOISI...a case of advanced Kuru, near-terminal, in a girl of about 6 yrs. who is on high daily doses of stilbesterol. She shows marked breast hypertrophy.

WARUYE (or Wara)...advanced, but still not near-terminal, Kuru in a boy of about 8-10 yrs. of age. He is on massive daily i-m doses of testosterone propionate.

35 mm still Film No. 12:

All shots taken in rapid succession on flight from Kainantu to Moke (Okapa) patrol post and on down valley of Okapa--Iagusa--Kasokana toward Lamari River.

Films show kunai-grass covered highlands gradually yielding to more forest-covered slopes of somewhat more rugged terrain as one travels south along the Jeep road from Kainantu to Moke Patrol Post. Villages are shown, including those on border of Kuru-non-Kuru regions. Kamano, Usurufa, Kanite, and Fore cultural and linguistic areas surveyed and shots taken of villages in each and of Moke-Okapa Patrol Post. Film exhausted over Lamari.

Extract from a letter from the Australian Museum dated 2 September 1957

In regard to the spiders, Mr. Musgrave reports as follows. The spiders forwarded have been identified as follows:

128. Obana. "Spider, small, black with white markings. Found in bush. Eaten only by small children. L. Hamilton."

The glass vial contained two large spiders: Cyrtophors mollucensis Doleschall, 1857. A species ranging from Java, Amboina (type loc) to New Guinea and Australia. A smaller spider, Leucauge sp., too mutilated to be identified with certainty. These two species are members of the family Argiopidae (orb-weavers).

150. Kogogora. "Spider, small. Found in bush and garden and kunai. Eaten by women and children only. L. Hamilton."

The glass vial contained three specimens representing three species, all members of the family Argiopidae. The largest of the three is Argyope aemula, Walckenaer, 1841; the other two species are members of the genus Araneus (Epeira).

It is interesting to hear of spiders being used as an article of food by the natives of New Guinea. La Billardiere in 1799 relates that the natives of New Caledonia eat certain members of the genus Nephila (a large orb weaving spider) in large quantities. He gave the name of Aranea edulis to one of these New Caledonian Nephila, although today it is known as Nephila edulis.

Okapa Patrol Post, via Kainantu
Eastern Highlands, Territory of
Papua and New Guinea
22 September 1957

(Roy, please excuse the carbon copy, but the original is so illegible because of poor ribbons, that I sent the carbon instead)

Dear Roy,

I have been completing the kuru epidemiology and finding the racial, ethnic and linguistic, as well as ecological limits of kuru by extensive patrolling, much of it through previously unvisited and "uncontrolled" territory. We find kuru involves somewhat more people than our original estimate, some 17,000 to 20,000 people living in the kuru region, with some one percent of all these currently affected with kuru, and dying. All but a very few of our first series of patients (since March) are now dead. Finally, neuropathological reports are beginning to arrive. From the U.S.A. (National Institute of Neurological Diseases and Blindness of the National Institutes of Health) we have reports of extensive neuronal degeneration in the cerebellum and anterior horn cells, with pontine nuclei, inferior olives, thalamus and extrapyramidal system also involved in the first six brains studied, and further studies are in progress. Toxic factors are still urged upon us, but we cannot find any signs of them, try as we may. We are probably just missing them in our study of the pica, diet nutrition, soil, smoke, body paints and, yet, genetic predisposition, at least, looms ever more likely from the field epidemiology and clinical studies.

A large shipment of blood specimens on the Kimi, from the very central Kimi tribe just beyond the border of kuru in a kuru-free region where there is a history of only one case in the past, and that "imported", went off to you. Thus, you have a fine racially pure non-kuru Kimi group, if the specimens arrive intact. In addition, I sent a series of specimens on the Papuan Yar people, which we managed to contact by exploring south of the Fore in the sago country. These are a sparse population, and you have over half the individuals in a region patrolled for over a week of hard walking, among the twenty-odd specimens we sent to you.

We had to send specimens back to Moke by the carriers, who walked twenty-four hours a day to get them placed in an icebox there, and thereafter have them taken out by jeep for air shipment to Australia. One box of venules remained, by being overlooked in the Moke icebox until our return. Thus, those twelve or so venules will be one to three weeks old by the time they reach you. Being valuable specimens, we rush them on. They have remained refrigerated all the time and it is still possible that some work with the cells, washed from the clots, will be possible; if not, discard them. I have sent these on to Lois to prepare for you. Enclosed you will find further copies of the lists documenting the Kimi and the Yar ethnic blood collections.

Also enclosed are the lists documenting the F Series of bloods, numbered 1 to 106, which I have just sent out to you. These are our definitive adult Fore blood collection, for comparison with kuru patients. They are from adult Fore,

all racially pure, without intermarriage, and all from a group of small adjacent tribes in the very center of the Fore linguistic and cultural areas, in the very center of the kuru region. Since every Fore is a blood relative of a kuru case, and since every Fore within a clan or tribe has some blood relationship with all others in the clan and tribe--because of intensive in-group marriage--we cannot avoid 'relatives'. However, in general, there is only one specimen per family group (father, mother, children). These specimens are for blood group study, normal Fore serum studies (Curtain et al.) and for infectious disease serological survey at a later date. I have identified subjects by sex and estimated age, place of clan affiliation, and the affiliation of mother and father of patients. All are pure-blooded Fore from central Fore territory, and from central kuru region; none are kuru patients.

We leave in a few days on the long promised Kukukuku patrol, and we may make an attempt to walk through from the highlands to the Papuan coast. Obviously, we shall be with populaces which, if we can get specimens, will never have been previously studied. Furthermore, since we are patrolling on this patrol the 'fringe' of the kuru region, and just beyond into kuru-free populaces, there is a great deal that may eventually be learned by comparison of all these peoples. Kuru has made it essential for us to have sound ethnological, linguistic and marriage pattern documentation of all the peoples we study, and this data, vast and voluminous as it is, fills my notebooks and can be supplied, once we call a halt to our kuru field work. I shall call a halt here, in order to get this out by the waiting jeep.

Sincerely and gratefully yours,

/s/ Carleton

P.S. I shall try in Moresby to dig up reimbursing funds to cover these expenses. Lois reminds me that we are indebted to you for all the supplies.

51.	Ninikabara	M 45	Iasubi	Iasubi	Iasubi	KIMI
52.	Faki L/L	M 44	Iasubi	Iasubi	Iasubi	KIMI
53.	Kagasia T/T	M 40	Awande	Awande	Awande	AWANDE
54.	Paiagasa	M 40	Iasubi	Iasubi	Iasubi	KIMI
55.	Pose	M 45	Iasubi	Iasubi	Iasubi	KIMI
56.	Tove	M 45	Iasubi	Iasubi	Iasubi	KIMI
57.	Omaigi	M 45	Miarasa	Miarasa	Miarasa	
58.	Oba	M 18	Iasubi	Iasubi	Iasubi	KIMI
59.	Kireiva	M 22	Iasubi	Iasubi	Iasubi	KIMI
60.	Taiosa	M 40	Iasubi	Iasubi	Iasubi	KIMI
61.	Karoyabu	M 40	Aga-Iagusa	Aga-Iagusa	Aga-Iagusa	AGAPA
62.	Amerasa	M 45	Iasubi	Iasubi	Iasubi	KIMI
63.	Kisare'wa	M 40	Awande	Awande	Awande	AWANDE
64.	Taiva	M 32	Miarasa	Miarasa	Miarasa	
65.	Ura'me	M 28	Miarasa	Miarasa	Miarasa	
66.	Kawaro	M 45	Awande	Awande	Awande	AWANDE
67.	Pa'e	M 45	Iasubi	Iasubi	Iasubi	KIMI
68.	Anunkavuta	M 20	Iasubi	Iasubi	Iasubi	KIMI
69.	Abusa	M 21	Iasubi	Iasubi	Iasubi	KIMI
70.	Tosi	M 18	Iasubi	Iasubi	Iasubi	KIMI
71.	Pirama	M 40	Iasubi	Iasubi	Iasubi	KIMI
72.	Ai'yo	M 21	Iasubi	Iasubi	Iasubi	KIMI
73.	Paeina	M 22	Iasubi	Iasubi	Iasubi	KIMI
74.	Nawari	M 30	Keakasa	Keakasa	Keakasa	KIMI
75.	Kupenota	M 18	Iasubi	Iasubi	Iasubi	KIMI
76.	Kanayabu	M 30	Iasubi	Iasubi	Iasubi	KIMI
77.	Aiyana	M 17	Wanitabi	Iasubi	Wanitabi	ATIGINA & KIMI
78.	Wanaiama	M 20	Iasubi	Iasubi	Iasubi	KIMI
79.	Yosaai	M 22	Keakasa	Keakasa	Keakasa	KIMI
80.	Isa	M 25	Miarasa	Mage	Miarasa	
81.	Tagona	M 25	Keakasa	Keakasa	Keakasa	KIMI
82.	Ona	M 28	Keakasa	Keakasa	Keakasa	KIMI
83.	Kaburotori	M 19	Wanitabi	Wanitabi	Wanitabi	ATIGINA (YAR cargo-b
84.	Uwane	M 16	Wanitabi	Wanitabi	Wanitabi	ATIGINA (YAR cargo-b
85.	Kokina	M 24	Okasa	Okasa	Okasa	ATIGINA
86.	Petaga	M 22	Kasoru	Kasoru	Kasoru	ATIGINA
87.	Atabu	M 21	Keakasa	Keakasa	Keakasa	KIMI
88.	Nonde	M 22	Kasoru	Uesa	Kasoru	ATIGINA
89.	Marebu	M 18	Mentirasa	Mentirasa	Mentirasa	IVAKI
90.	Agasa	M 17	Keakasa	Keakasa	Keakasa	KIMI
91.	Nago'tne	M 14	Takai	Takai	Takai	IVAKI
92.	A'eta	M 22	Keakasa	Keakasa	Keakasa	KIMI
93.	Ikiyamo	M 26	Amora	Amora	Amora	ATIGINA
94.	Togabara	M 17	Keakasa	Keakasa	Keakasa	KIMI
95.	Tasa	M 18	Keakasa	Amora	Keakasa	ATIGINA & KIMI

96.	Pake	M 30	Wanikanto	Kamata	Wanitanto	ATIGINA & WANTAKABAR
97.	Igaga	M 21	Keakasa	Uesa	Keakasa	ATIGINA & KIMI
98.	Ikasu	M 26	Wanikanto	Kamata	Wanikanto	ATIGINA & WANTAKABAR
99.	Ieku	M 15	Mugaiamuti	Mugaiamuti	Mugaiamuti	PUROSA
100.	Kogosa	M 22	Okasa	Okasa	Okasa	ATIGINA
101.	Kambe	M 18	Mugaiamuti	Mugaiamuti	Mugaiamuti	PUROSA
102.	Ainita	M 40	Okasa	Okasa	Okasa	ATIGINA
103.	Inta	M 25	Agakamatasa	Agakamatasa	Agakamatasa	WANITABI
104.	Atenta	M 19	Mentirasa	Mentirasa	Mentirasa	IVAKI
105.	Yawari	M 17	Keakasa	Keakasa	Keakasa	KIMI
106.	Ireve	M 19	Agakamatasa	Agakamatasa	Agakamatasa	WANITABI
107.	Paru	M 23	Yau (Yar)	Yau (Yar)	Yau (Yar)	<u>YARAVANA</u> <u>PEOPLE</u>
108.	Maiari	M 25	Weme (Yar)	Weme (Yar)	Weme (Yar)	<u>YARAVANA</u> <u>PEOPLE</u>

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
September 25, 1957

Dr. Theodore H. Ingalls
Associate Editor
The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

Dear Dr. Ingalls:

I have a copy of Dr. Smadel's letter to you of August 28, referring to the paper by myself and Dr. V. Zigas on KURU. I assume that you have already received, in addition, a selection of photographs of the Kuru region and of Kuru patients from which to select illustrations for the article.

I am writing to request a few minor additions and changes in the paper since it is possible that I may be unable to do any galley proof correction prior to publication in November. This letter is being forwarded to Melbourne (Walter and Eliza Hall Institute of Medical Research), Australia, where definitive copies of a map showing the location of the Kuru region are being prepared. It will be mailed to you from Australia along with glossy prints of the map which, I hope, arrives in time to be included as Figure 1 in the article. Geographic localization is of much importance in Kuru epidemiology. Furthermore, the map will greatly aid the reader. The map is itself self-explanatory. If a further legend is desired use:

Figure 1. Map showing location of the Kuru region in the southern portion of the Eastern Highlands of New Guinea.

In addition, I would like to request that the pathological findings which Dr. Smadel supplied to you in his letter of August 29th, be placed within the body of the paper rather than as an Addendum, as he suggested. In the revisions I previously mailed to you (July 26) I already brought case figures sufficiently up-to-date to embrace all cases thus far examined neurohistologically. Thus, I suggest including the same description Dr. Smadel furnished to you with the introductory word "However", as an added three short sentences which can be inserted into the text on page 4, just after the sentence which ends on the next to last line of that page, i.e. "Histological and neurohistological findings will be reported (Insert) "in detail" in a further communication. (Insert) "However, the preliminary pathological study of six cases reveals a widespread neuronal degeneration.

The cerebellum and extrapyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus, and pontine nuclei."

Dr. Smadel will shortly inform me of the film negative edge numbers of the photographs he has selected from our Kuru film file for the paper. From these I can identify the photographs and promptly write captions which may be used should they differ significantly from those Dr. Smadel has submitted. He has attempted the task under the disadvantage of not knowing the case depicted, and it is possible that pictures may have been inappropriately described.

Finally, I should like to insert the following brief text at the very end of the paper. The pathological findings just recently made available to me in no way change any of the facts we report, but they do influence somewhat the stress and interpretation thereof. It thus behooves us to recapitulate our strong suspicions of toxic or post-infectious factors, in spite of our inability to demonstrate them. Thus, please insert before the bibliography and after the last word in the current manuscript on page 8 the following brief lines:

" The extensive neurological degeneration found on histological study strongly suggests some toxic factor. Thus far search for such factors in diet, pica, skin painting, smoke and other sources has failed to reveal any organic agent which might be responsible for the disease and trace metal studies on blood, urine, cerebrospinal fluid, and other pathological specimens from Kuru patients and on foods, soil, water and fire ashes have failed to indicate any heavy metal intoxication. If the degeneration of Kuru is a post-infectious phenomenon the antecedent illness must be so mild or subtle as to escape detection by the Natives and ourselves."

I am sorry to bother you with these further changes, but in the light of this added data, which greatly improves the paper, I believe, they become mandatory.

Sincerely yours,

D. Carleton Gajdusek, M.D.

P.S. Since completing your letter, mail has come in with several letters from your office. We are glad to learn that the paper will soon be published and trust that the map will arrive within two to three weeks after receipt of the photographs from Dr. Smadel, along with this letter. By that time I hope to have captions for the photographs to you. The change in title suggested is satisfactory to us. Perhaps, however, the word Natives should be inserted after the word New Guinea in the title, as suggested by you. Thus, it should read:

-3-

Degenerative Disease of the Central Nervous System in New
Guinea Natives: The Endemic Occurrence of "Kuru"

Enclosed you will find the two cards you sent to be filled out by
Dr. Zigas and myself.

Sincerely, .

D. Carleton Gajdusek, M.D.

Okapa Patrol Post
via Kainantu
New Guinea

15th October 1957.

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland
U.S.A.

Dear Dr. Smadel,

Lists of identifications of many of the foods eaten by Fore people have come to hand. I shall forward you these lists and perhaps from them a lead may be obtained as to foods which contain toxins which could cause kuru.

These lists are not yet complete. I still have specimens which have not as yet been identified.

Most of the insects are eaten only by women and children, but non-kuru from Fore and other regions eat them as well as kuru sufferers. It could be that those who develop kuru eat more of a certain species than others, but they do not obtain these foods when in hospital and appear to eat very few insects after the onset of kuru.

It has been pointed out by the entomologist that some of the insects grouped by the Fore people under the one name belong to several different species. It is perhaps possible that those people who develop kuru eat a species which may contain toxins, and other people eat a species which do not contain those toxins but both species are known by the same name by the Fore people.

There are many varieties of fungus which are eaten in considerable amounts by everybody, that is, kuru sufferers, non-kuru Fore people and people from other areas where kuru does not exist. These fungi have not as yet been identified.

I am collecting specimens of medicinal plants. There are very few which are commonly used even throughout the Fore area. Most are very localized, that is, known of only in one village or by a few old men in that village. I have been told of some, but few people seem to have used them.

I have made lists of all foods eaten, and am questioning kuru patients, non-kuru Fore people and people from other areas as to the foods commonly eaten. From this I should be able to discover whether there are certain foods that kuru sufferers have been in the habit of eating more than other people. When completed, I shall send you results of these investigations.

Yours Faithfully,

Lucy Hamilton

Foods Eaten by Fore People

Botanical

Fore Name

Botanical Name

Pumpuina	Pulchea? Compositae.
Tosowaria	Compositae Bideus sp.
A'moya	(fern)
Pupaiya	(fern)
Kokum (dye chewed and spat onto string)	Coleus sp.
Isi	Ficus sp.
Makka	Compositae Lactuca ?
Pika	Phophocarpus tetra gonolobus.
Na	Compositae.
Pumu	Impatiens sp.
Moa	Impatiens sp.
Orepenia	Desmodium sp.
Make	Gleichania sp.
Waisa	(fern)
Akinamunta	(fern)
Apa	Finschia
Kegeta	Desmodium sp.
Kaine	Zingiber Officinalis
Karosa	Piper sp.
Asi	Broussonetia sp.
Towa	Dammaropsis kingiana
Ebia, Kaninta	Acanthaceae Ruellia sp.
Akanu	Oenanthe Javanica
Akinamunta	(fern)
Ne	Commelinaceae Pollia sp.
Pupum	Solanaceae Solanum sp.
Arikoko	Phaseolus sp.
Kabasoso	Phaseolus sp.
Warie (used as wrapping for food whilst cooking)	Cordyline sp.
Kaia	Cucurbitaceae.
Mebe	Rubus Rosaifalius.
Karakaronta	Rubus Ledermann
Wabanona	(fern)
Orskia	(fern)
Karu	Elaeocarpaceae Elaescarpus sp.
Kekna	Hibiscus?
Yato	Asplenium sp.
Meine	Amaranthus sp.
Kimoni	Cucurbitaceae.
Apaya	Monimiaceae Palmeria ?
Amunta	Piperaceae Piper sp.

Ompakara
 Agonomea
 Kilisa
 Sepo
 Awasa
 Munta
 Kagine
 Kara
 Yaka
 Arane
 Ereriba
 Komukomei
 Wako
 Kaetawa
 Keo
 Tabi tabi
 Wapa
 Purri purri
 Ina
 Teresewa
 Pia
 A'oria
 Anusara
 Tarakeia
 Yalisa'akoya
 Kapasarani
 Kosa
 Petu
 Meyo
 Kimisi
 Manino
 Tope
 Montaga, nonee
 Na'mei
 Iga
 Nawi
 Entabina
 Kusa
 Umba'aro
 Poma
 Igila
 Taraine
 Takai

Phaseobos sp.
 Elatostemma sp.
 Palmae acera sp.
 Palmae acera sp.
 Begonia sp.
 (fern)
 Acanthaceae Pseudonthemum.
 gramineae - unplaced genus.
 Phaseolus lunatus
 Cruciferae brassica ?
 Amaryllidaceae, euryeles sp.
 (fern)
 Podocarpus Pamarus ?
 Ricinus Communis
 Ficus sp.
 Irisene sp.
 Zingiberaceae.
 Asplenium nidus.
 Pandanus pseudopapuanus ?
 Acanthaceae Bauleria ?
 Pandanus pseudopapuanus ?
 (fern)
 Elatostemma sp.
 (fern)
 (fern)
 Pandanus Krauelianus
 Pandanus
 Compositae Erechites sp.
 Piper sp.
 (tree fern)
 (fern like)
 Palmae acera sp.
 Euphorbiaceae neoscortechina ?
 Amaranthus sp.
 Convolvulaceae
 Physalis peruviana
 Begonia sp.
 Laportea sp.
 Pipturus repandanus
 Elatostemma sp.
 Elatostemma sp.
 Pipturus sp.
 Ebenaceae.

Insects

Fore Name

Entomological Identification

Atataria	Moth larvae-one of the sugar cane boring moths.
Obana (spider)	Cyrtophora molluccensis, Doleschall and Leucauge sp.
Kogegera (spider)	Argiopidae sp., Argiope aemula and Araneus genus.
Iloni	Short horned locust, fam. Acridiidae, Valanga sp.
Siskbamu	Long horned grasshopper, fam. Tettigoniidae.
Abi	Larvae of Cerambycidae (Longicorn)
Eeo	Small sp. of Tettigoniidae.
Nantutoria	Fam. Mantidae. egg kasinkom also eaten.
Pretoma	Fam. Gryllidae.
Kabo	Nymph of field cricket, fam. Gryllidae.
Karakaba	Large stag beetle. Fam. Lucaniidae.
Kariko	Larvae of scarab beetle, Lipidiota sp.
Inokaba	Black weevil, fam. Curculionidae.
Kanunta	Moth larvae.
Tabatoria	Airidiidae, similar to "Iloni".
Milaeia	Rosechafer Scarabidae.
Amueeo	Fam. Aridiidae, one of the shorthorned locusts.
Kabane	Lepidiota sp. similar to adult of "kariko".
Tobogoba	Longicorn beetle fam. Cerambycidae.

October 31, 1957

Dear Miss Hamilton:

Thank you very much for sending us the list of foods eaten by the Fore people. I have circulated copies to those here at the National Institutes of Health who have been working on materials sent us by you and Dr. Gajdusek. Dr. Horning in particular may have some helpful comments on some of the foods listed.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Miss Lucy Hamilton
Okapa Patrol Post
Via Kainantu
New Guinea

cc: NINDB files

CGBAKER:smh

MF-NIH-PHS-1958

7584546

18408-51

Typed 9:15 a.m.
October 21, 1957
Bethesda, Maryland

DR. D.C. GAJDUSEK
DR. LUCY HAMILTON
OKAPA PATROL POST via KAINANTU,
EASTERN HIGHLANDS
TERRITORY OF PAPUA AND NEW GUINEA

INVESTIGATIONS ON PLANT MATERIALS RECEIVED FROM HAMILTON
INDICATE PIT-PIT SAMPLES NUMBERED 6, 7, 11, 13, 14 and 15 AND
AGARA STRONGLY POSITIVE FOR ALKALOIDS. OTHER PIT-PIT SAMPLES
SLIGHTLY POSITIVE. KEGETA 38 AND EREREBA NEGATIVE FOR ALKALOIDS.
ARRANGING FOR BIOASSAY AND TOXICOLOGY. NEED 5 POUNDS EACH AGARA
BARK AND LEAVES. NEED 10 POUNDS KEGETA 38. NEED PIT-PIT BOTANICAL
SPECIMAN WITH FRUIT AND 5 POUNDS EACH OF PIT-PIT SAMPLES 14 AND 15.
CAN YOU REPEAT NATIVE FEEDING EXPERIMENT WITH EREBEBA AND AGARA
GIVEN SEPARATELY AT CONTROLLED DOSES? USDA TAGS FOLLOW AIRMAIL.

SMADEL

cc: NINDB Files

October 21, 1957

AIR MAIL

Dear Carleton:

Enclosed are some additional tags to be used in conjunction with your sending plant material to us and a copy of the cable gram which I hope you have already received.

The identification of the specimen sent earlier, family Araceae, genus Homalomena, has been confirmed for one of the specimens sent by Lucy Hamilton. The reaction of the man who had eaten Erereba and Agara, as described by Miss Hamilton, has stimulated high interest among some members of the staff of the National Institute of Mental Health. It is this group, headed by Dr. Seymour Kety, who will attempt to establish a suitable bioassay method to be used in conjunction with Dr. Horning's chemical isolation and fractionation studies. Furthermore, it is possible that the staff at the Addiction Treatment Center in Lexington, Kentucky, might wish to test some of the crude material in human subjects if toxicology studies indicate this is feasible.

As indicated in the telegram, we are requesting 10 additional pounds of Kegeta 38. Dr. Horning has requested this even though it is negative for alkaloids because according to the information sent with the plants this material is eaten by the population group suffering from KURU, but not by other groups in the area. He proposes that extensive workup be made in an attempt to obtain clues in relation to KURU.

I hope these requests do not overtax your group with the limited facilities available. Some of these materials look very interesting, and we hope to obtain information that will make your efforts required for sending the materials worthwhile.

Sincerely yours.

/s/Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu, New Guinea)

Enclosures

October 29, 1957

AIR MAIL

Dear Carleton:

I am enclosing for your information copies of two memoranda. From Dr. Kurland's memorandum it is evident that he has a lively interest in kuru. Perhaps you will find his ideas of interest, and on your return to the States I am sure you will wish to talk with him.

The other memorandum is from Dr. Horning, and it confirms the information sent to you by cablegram.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu, New Guinea)

Enclosures (2)

cc: NINDB files

CGBAKER:smh

October 18, 1957

To: Dr. Joseph E. Smadel, Associate Director, NIH
Thru: Acting Director, NINDB
From: Chief, Epidemiology Branch, NINDB
Subject: Kuru

Thank you for the copies of Carleton Gajdusek's letters of September 22 and 27 which were reviewed. In his previous letter, Dr. Gajdusek mentioned that the Fore people are well nourished and that food was not in short supply. Perhaps cannibalism has some hidden meaning, but when I learned that grandpa or someone else was occasionally served for dinner, and that spiders and other insects were eaten by women and children, I wondered if a large segment of the population isn't barely surviving and if the best food available doesn't go to the man of the house.

I note that Dr. Gajdusek is going to tremendous trouble to obtain blood specimens; if these are for genetic typing I seriously doubt that they will tell him very much except the blood groups of the Fore people and little if anything insofar as distinguishing the affected from the unaffected in this inbred population.

Speculation of a diffuse neuroectodermal hypersensitivity developing because of the ingestion of human tissue is interesting, but I believe only a remote possibility. The isoallergic phenomenon can be induced only with the greatest of difficulty unless adjuvants are used and the material given by injection. Furthermore, I would suppose the men rather than women and children would be most likely to partake of such a feast.

The study of spiders (and perhaps other insects and odd plants) sounds like a good lead since, for the first time, he has found some selectivity in diet for the group principally affected. I haven't had any experience with the toxic qualities of spiders, but Dr. R.E. Crabill of the Smithsonian Institute informs me that a few of the species mentioned are said to be used for food by natives in South America and Thailand but that several of the species mentioned by Gajdusek are unknown to him. Feeding experiments of freshly ground spiders and other local insects in monkeys or other animals were suggested. In addition to the possibility of ingested toxins, I suppose one could be bitten occasionally when trying to capture spiders and the species in New Guinea may be different from those which the authorities on the subject have heard about before. However, it is unlikely that spider eating is a newly developed practice here and it would be difficult to explain a new disease unless a new practice was introduced or a genetic mutation had occurred in the rapidly reproducing agent (spiders, etc.) rather than in the Fore host.

I hope that Dr. Gajdusek will have the opportunity of meeting with us when he arrives at the NIH, for we would like very much to have him tell us of his fascinating experiences.

52b enclosure

October 22, 1957

To: Dr. Carl Baker

From: Dr. E.C. Horning

Subject: New Guinea Plants

The plant samples are being identified, and we should have an answer this week. A fruiting specimen of "Pit-pit" may be needed for species determination.

The tests were as follows:

<u>Sample</u>	<u>Alkaloid Tests</u>	
Kegeta No. 38	-	-
Kasinkom	Insect cocoon, not passed by inspection	
Pit-pit (16 varieties)	+++	+++
Nos. 6,7,11,13,14,15		
Ereriba (<u>Homalomena</u> sp.)	-	-
Agara Leaves	+++	+++
Bark	+++	+++

When positive alkaloid tests are obtained, it is best to make the assumption that the physiological activity, if any, will be due to the alkaloid content. We can therefore use chemical tests to obtain samples for physiological examination in the case of Pit-pit and Agara.

For Kegata No. 38 and Ereriba (Homalomena sp.) isolation studies require a bioassay.

It would be desirable to know if Agara and Ereriba produce effects on humans when used independently.

I will let you know about the identifications as soon as I have them.

52c appendix

October 28, 1957

To: E. C. Horning, Chief
Chemistry of Natural Products Section

From: B. G. Schubert, Botanist
Plant Introduction Section, CRD

Subject: New Guinea plants

Thank you for your memorandum of the 22nd with results of alkaloid test on New Guinea plants.

As I told you over the phone Kegeta no. 38 is a *Desmodium*, probably *D. dasylobum*, not a common species. If there is a possibility of getting better herbarium material I should like it for my own studies on the genus.

Pit-pit is a grass in the genus *Setaria*. There is no material at the Smithsonian which quite matches what was sent. More material, especially of the wild variety (no. 16) in mature condition, would be very desirable.

The Erereba material was not adequate for a better determination than before, but we should like more material of whole plants with the flowering spike and base if possible.

Agara is extremely interesting botanically since it is a member of the Himantandraceae, a family with only 1 genus *Himatandra*, and probably only 1 species, *H. belgraveans*. This genus is endemic to New Guinea and Australia and is important from an evolutionary point of view. We should be very pleased to have more botanical material.

BGS:pf

cc: Dr. Carl Baker

NOVEMBER 3 1957
PORT MORESBY

SMADEL
INSTITUTES
BETHESDA
MARYLAND

MED 3246 KURU ILLUSTRATIONS NOT RECEIVED MEDICAL JOURNAL OF AUSTRALIA
AS OF OCTOBER 17TH STOP PLEASE CHECK STOP

GAJDUSEK

Port Moresby
...in the throes of our Kuru Conference
Territory of Papua and New Guinea
November 4, 1957

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland

Dear Joe,

This letter contains many things which require fairly prompt attention and thus, I apologize at the onset for the numerous requests and the delay in getting them to you and in supplying you with much information.

Only a few days ago I came through to the sea--the Papuan Coast--after descending the Lamari (Subu) into the Purari and thus "crossing the island" with a group of natives who had before this trip never rafted, canoed, nor seen salt water. Before we knew it, we had "made history" and National and Territorial radios were reporting an exploit--often highly dramatized and exaggerated--which in the patrol seemed only a pleasant excursion. Having thus "made history" I am only now discovering the appalling journalism that broke over our heads while I was out of all contact with civilization for over six weeks with the wonderful Kukukukus and finally, descending southward from the Highlands, through sago country, the Pawaian peoples of the Upper Purari and down the mighty waters on raft, canoe and larger canoes to the coast.

Enclosed are a set of Australian newspaper clippings that have been sent up to me--all nonsense and appalling--but only the beginning of a real barrage of sensational journalism which is about to hit us, I am told. Furthermore, during my absence, the Australasian TIME and LIFE representative camped with Vin Zigas, waited and waited my return from the wilderness and finally gave up when word reached them--which I had sent from my patrol--that I was heading deeper and deeper and further south rather than returning to Okapa. Thus, I am told, any day a US "story" may appear and I cannot vouch for a word of accuracy and I am most disturbed. However, a Catalina was sent to pick up our patrol, telegrams went out to Vin Zigas and Lucy Hamilton and Smythe (who has worked with us medically and on Fore linguistics) and I managed to have a "Kuru Congress" organized here only a few days after emerging from the bush.

Patrolling has fully established the geographic extent and limits of Kuru and the cultural affiliations, cultural spread, native trade routes, and marriage contacts of the Kuru-afflicted Peoples and this immense task of 1500-2000 miles of some of the hardest walking in the world is now done!!!!

Proofs from the NEJM article have arrived but obviously it will be out before I can reach them by mail and since I trust you picked up the misspelled Fore (spelled Forei in the first paragraph of the paper) and other minor corrections, I am most satisfied. The sooner it gets out the better, now that the press has garbled up the story from misinformants.

The Australian article is all ready for press but the arrival of glossy prints for appropriate illustration has failed to materialize. I asked you some time ago to send such retouched glossy prints to them as soon as possible and the matter now becomes an emergency, for the press there is making shambles of the matter and a definitive medical report must immediately appear in the Australian journal. Editors of The Medical Journal of Australia (Ronald R. Winton, Editor, Seamer and Arunde Streets, Glebe, Sydney) telegraphed me today that they are still anxiously awaiting these illustrations from you. If, by any chance, you did not get the letter in which I requested them, listed the specific shots and sent full request that these be prepared and sent to the Journal, please let me know immediately by cable. If you did get the request and can hurry up the dispatch of these photos to Sydney, please do so. If, on the other hand, something has gone wrong and my request has gone astray, then select 8 (eight) of the best pictures...at least 5 or 6 of patients and 1 or 2 of Hospital, background, etc. and send them instead--since here in Moresby I lack the prints to look through again for choice or the letter files to find my previous choice. You must have received the original request, however, and I suspect delay is just in photo processing or in mail. If mail is the matter and there is any chance of loss, can new prints be rushed to Sydney and the editor informed by cable that they are coming and that others are en route (or perhaps lost in transit).

This, then, will complete the first two preliminary reports, satisfy US and Australian crowds, and leave us time to prepare definitive studies. Klinische Wochenschrift has, by the way, accepted for publication the 3rd, much more definitive paper, and I am now revising that and bringing it up to date for a really good German article, which will be the most complete report on Kuru (the 3rd in medical literature). The final definitive studies I shall write from the U.S.

We have just had visits by Prof. Eccles (Australian National University-Canberra), one of the World's foremost neurophysiologists; Prof. of Medicine H.N. Robson of Adelaide, and Prof. Sunderland, neuroanatomist from Melbourne, and the three, after spending only 1½ days at Okapa and seeing only 9 patients --for in my patrolling in the bush we have let the clinical side and case collecting lapse--of our series, are beside themselves with enthusiasm and they state that without any doubt this is the most important neurological discovery of decades. They apostrophize and hyperbolize at length, but the gist of the matter is that they are rushing back to Australia with the story and Eccles says that he would have dominated the International Congress of Neurology in Brussels with the Kuru story and that the entire new gamma-fiber story of motor neuron function would have been dominated by Kuru had he only known about it. He sees the possibility that the new gamma-fiber concept and theories may line up with the lesions in Kuru very closely. It may well be that this absolutely unique type of "tremor" and incoordination is primarily a disturbance of the gamma-fiber radiations. At any rate the Professorial

delegation thought Pearce Bailey should be in on Kuru immediately...I told them that through you he was. They thought Denny-Brown should fly out at once! They thought that the entire neurological world had in Kuru its choicest and most promising problem.

Finally, with us, they believe that some toxic factor must underlie the process and our continued suspicion of a trace metal imbalance, toxicity or deficiency looms most likely...especially in view of the Wilson's disease story, Manganese poisoning (Moroccan miners), and Mercury (chronic) neurological lesions. We mused about Vanadium, Molybdenum, Zirconium, Tungsten, and a host of others and must admit that slow chronic poisoning or sudden massive insult with progressive degeneration even after contact was stopped, were possibilities we had not eliminated or even investigated and that continued study through the periodic table of all tissues and fluids on hand was the most urgent matter. Thus, I am now writing to beg you to conserve aliquots of whatever is on hand, to not exhaust them on any one metal study, and to do all possible to get wide screening for trace element deficiency, or, more likely, poisoning. It is true, that Kuru occurs in a mineral rich part of the world, near massive heavy metal deposits (gold, nickel, etc) and between two great River drainages (Yani and Lamari) and not beyond these two!!! Although soil or water mineral contamination (or deficiency) would not explain age, sex distribution, there may be some other subtle environmental or cultural factor that does...even, perhaps, endocrine, and the trace metal possibility still seems most probable of all the toxic suggestions.

We are still pursuing ethnobotany, tracking down botanical and entomologic species of all the specimens eaten. Erereba, the Kuru-tremor plant does not produce tremors or marked reactions, such as Lucy described to you, in a few other Natives and Europeans who have tried modest doses. However, the Natives remain adamant in their story of its effects and further experimental trial will be done when I get back to Okapa. It remains an interesting plant. We are wondering about a mycotoxicosis and other possible toxicities resulting from food spoilage or storage, but cannot yet pin any such event upon Kuru diets, or even on the age and sex group most affected. Shortly the zoological and botanical taxonomic lists of Fore and Kuru patients diets, pica, skin exposure, etc. etc. will be off to you for survey by any and every "expert" who might be able to spot in the huge list of genera and species interesting toxic possibilities.

Trace copper studies on Kuru and control bloods done at CSIRO in Melbourne seem to rule out the possibility of gross copper poisoning. Other metals have not been looked for extensively as yet and I doubt if the CSIRO group will ever. Trace metal-free brain--sent to you--was unique, and we certainly hope every conceivable cytochemical and histochemical and trace metal study will be done on it. Two other "trace metal free brains" are fixing now and will shortly be off to you. We gave Prof. Sunderland of Melbourne one Kuru brain. Others will shortly be off to you.

I hope to send out in the next few days the immense file of 'trace metal-free blood, tissues, and especially, CSF which has been stored in ice boxes here in Moresby, unstudied. This is a completely unreplaceable collection representing a half-year of field work, and it cannot easily be repeated. Since it looks as though nothing can or will be done on it in the near future here, I am sending it all to you, refrigerated, and I hope that the chemists and NINDB groups will do justice to the immense effort which went into collecting this series of specimens.

Reprints? I did not order from NEJM on time. Did your group order enough for Vin and me to get a small stack each? If not, my order sent in today might (???) arrive on time. I hope so. Will NIH order reprints of the Australian and German papers?

My plans: The 100-odd currently active cases (our series is now of close to 200 patients, well over 50 of whom have died) must now be rapidly relocated, reevaluated, and restudied. Those who can be brought in will be given further clinical therapeutic trials, especially of calcium versenate or other chelating agents, and of any other drugs we can get in the next few weeks. We shall do everything possible to get further blood, CSF, blood films, autopsy specimens and ethnobotanical collections and food, soil, fire ash, etc. specimens together and off during the next few weeks. Then I shall leave and wend my way back to the U.S. with the firm intention of continuing on the Kuru problem. First in analysing the records, the films, the epidemiological files and writing the appropriate reports; secondly in taking some part in the laboratory studies, and finally, in planning a return attack in a year or so, on the Kuru problem which must be cracked!! I like the possibility of being placed for a period of months as "Visiting Scientist" at the NIH when I return, for as you know I am fully without income now and have been and the NFIP grant was for only \$1000-- in spite of their misstating that it was for \$2000 in a recent letter to me re reprints of the articles. Any prompt and immediate source of income upon my return may help get me out of the hole that I am sinking into as I continue to work on Kuru. The "job" will let me get the paper writing done, the data analysis complete, and give me time to "look around" for something more permanent... that it must permit a continued interest in Kuru is sure.

I am told by Vin that further cine film was sent and is awaiting me at Okapa. The last 6 rolls of 16 mm Kodachrome are "travelogue" and background anthropology from the beginning of this last venturesome patrol. We bought and paid for that film, including for all developing which, therefore, you in the U.S. should not again pay for since Kodak in Australia has already collected for the full processing, anywhere, and I felt that this patrolling into "new country" fully justified the use of the film as we used it. Here in Moresby I am now cutting and editing and preparing a sound track on 25-30 minutes of fairly good black and white film on the clinical picture of Kuru and this "professional" film will be off in a 16 mm copy to you very shortly. Actually, I have full permission to use any portion of it we wish in a final, definitive, longer Kuru picture, covering every aspect of the illness including serial follow-ups on individual patients in time, as the disease progressed. We shall try to use cine film liberally in our final spurt of Kuru work which we are about to launch. It appears, furthermore, that there will

not necessarily be a lapse in clinical follow-up. The Australians are very impressed and are trying to prepare a clinical field team to take over my records and follow all of our cases upon my departure. I have secretarial help now in preparing copies of all active case records to leave behind for them, and thus, with luck, there may be a chance of continued and uninterrupted clinical follow-up of Kuru. Professor Robson himself wants to bring up a team for the further clinical follow-up and therapeutic trial study of the disease.

Since our remote patrol post cannot sustain any larger numbers, the Government will have to, it appears, limit investigators interested to those it invites. I am ensuring our return, by arranging for it now... and all is in complete agreement here. Our visiting professors were most frantic lest fire wipe out our newly-constructed, thatched Kuru-house with its completely unreplaceable stacks of records and, taking this warning, I shall soon start shipping them off to you for file pending my return. Copies of active case records will be made and left here for further follow-up study.

This then should bring you up to date on Kuru, Joe. I cannot make Bangkok, for Kuru is more important. I shall, however, be off very shortly, and although my route home must be a long one, I am heading directly for NIH and I shall stick with the paper writing until we have milked the records dry and with Kuru until we have solved it. AICF studies are too big a thing, I realize. I shall be interested in seeing what others are doing with them, -- perhaps, even they may help in Kuru--but Kuru comes first. If that passes, AICF leaves plenty to do. Furthermore, I am brimming with new projects which I shall keep bottled for the moment. If, by any chance, you or anyone else can fly in to see Kuru during the next few weeks (en route to Bangkok or some such venture) let me know immediately by cable. After my departure there will be another lapse for a while and few cases on hand for demonstration to a passing visitor.

The Australians are, understandably, most anxious to get our Kuru article out. I beg you to do everything possible to get the glossy prints for illustration off to them...otherwise, we shall have a hefty "international incident" on our hands.

Sincerely,

Carleton

P.S. Please hang on to all the enclosed clippings in the "Kuru Files."

RECORD OF CINE FILMS - 16 mm - taken on Bolex H-16 Camera supplied to D. Carleton Gajdusek, M.D. by NIH, Bethesda, Maryland.

Films No. 13-18....all Cine Kodachrome, Daylight type. All Australian-bought film with processing already paid for in Australia when film bought.

Films taken on Kuru Research Epidemiological patrol through Kukukuku region.

FILM NO. 13:

Exposed September 28, 1957 Iakeia. View across the Lamari from Iakeia toward Mobuta.

Exposed September 29, 1957 Crossing Lamari River with cargo on tree-rope bridge between Iakeia and Mobuta.

Exposed October 1, 1957 Agamusei. Building camp.

FILM NO. 14:

Exposed October 1, 1957 Agamusei. Building camp. Agamusei Native boys. ("mabis"...initiated).

Exposed October 4, 1957 Auroga...Kukukukus

Film taken in fortified, stockaded village of Ureba. Women and children outside of women's house. Men at men's house.

FILM NO 15:

Exposed October 6, 1957 Auroga. Filmed at fortified hamlet of Ureba showing women and children, old woman smoking native pipe. Woman with yaws ulcer of sole of foot. Men at Men's house. View of Kanewabi hamlet from Ureba.

FILM NO. 16:

Exposed October 4, 1957 Auroga...Hamlet of Ureba. Kukukukus.

Exposed October 5, 1957 Auroga...Shields taken from house in village of Igopiji. Views of village of Kuanimugu from Igopiji. Party setting off for Kuanimugu from Igopiji. View back toward Igopiji.

FILM NO. 17:

Exposed October 5, 1957 Auroga...View from Kuanimugu. Towards Wantikia

Exposed October 11, 1957 MUNIRI Kukukuku hamlet of Kandui...group of Muniri Kukukukus.

Hamlet of Yau'ui...Kukus at men's house. View toward village of Nanjau (Muniri).

Close up of Kuk boys at our Miniri camp--Maiguaga hamlet.

Exposed October 14, 1974. Moraei...

Exposed at Wacheraminti hamlet of Moraei.

Women in front of houses in garden hamlet. Infants playing.

Boys of Watcheraminti

FILM No. 18

Exposed October 14, 1957. Moraei.

Exposed at Watcheraminti hamlet of Moraei.

Women and children in front of houses in garden hamlet.

Boys of Watcheraminti, Boy stringing and unstringing bow.

Close up of one woman cutting hair of another with bamboo knife.

Shots--close-up--of boys of Watcheraminti. All Kukukukus.

All films shot at 24 frames/second and without using any filter.

54a appendix

5th November, 1957

Dr. Pearce Bailey,
N.I.N.D.B.,
National Institutes of Health,
BETHESDA, Md. U.S.A.

Dear Dr. Bailey,

I have just returned from visiting New Guinea where I met Dr. Gajdusek and had the opportunity of visiting the area where he has been working on this extraordinary disease, Kuru. I am enclosing the official report that we made as a result of our visit so that you can see how highly we regard the work that he and Dr. Zigas are doing. I feel that this disease is the most interesting neurological disorder that has been found in recent times and it is worth the most intensive possible investigation. I know that your Institute has been giving him very good support and I would like to let you know how much he and Dr. Zigas are appreciating it because up to date, for reasons that we need not go into, Australian help has been negligible. I have come back from New Guinea fascinated by the problem and full of admiration for the heroic efforts of Drs. Gajdusek and Zigas. What they have done there is simply magnificent, and to me and to my colleagues it was a thrilling experience to go there and see, at first hand, what had been done. You will probably have Dr. Gajdusek back in Bethesda in the near future for a brief visit, but I think you will find that he will return there at the earliest possible moment as his emotional attachment to New Guinea and this problem of Kuru is so great.

It was very nice meeting you in the Summer and seeing all your interesting exhibits relating to Sir Charles Sherrington. I have been meaning for some time to write and ask you if you had any spare copies of your photographs of his letters. I would be very glad to have them. I have many of his letters here, mostly about personal things, but there are several that you might like to have copies of. If so, I would be happy to have them copied here and send them to you.

My very best wishes,
Yours sincerely,

(J.C. Eccles)
Professor of Physiology

REPORT ON THE KURU DISEASE

By

H.N. Robson, Professor of Medicine, University of Adelaide; S. Sunderland, Professor of Anatomy, University of Melbourne; and J.C. Eccles, Professor of Physiology, Australian National University, Canberra.

At the invitation of Dr. Scragg, Director of Public Health for the Territory of Papua and New Guinea, we visited the peoples that are afflicted with the disease that is known by the natives as Kuru.

We arrived at Kainantu on Wednesday, October 30th at 10:30 a.m. and were met by Dr. Zigas, the District Medical Officer. After visiting Kainantu Hospital and examining two Kuru patients there, we were driven by Dr. Zigas to the Patrol Station of Moke in the midst of the Fore linguistic group, arriving at about 3 p.m. On the way there we examined one advanced case of Kuru in a native village. At Moke Hospital there were nine cases of Kuru assembled for examination. The whole of Thursday was devoted to a thorough clinical examination of those nine cases, which were at various stages of the disease. We left Moke at 7 a.m. on Friday, November 1st, and have had since then the advantage of a prolonged discussion with Dr. Gajdusek and Dr. Scragg at Moresby, and we have also seen there the film prepared by the National Film Unit. Furthermore, we have closely studied the papers written by Drs. Gajdusek and Zigas and the very careful and extensive case reports that they have prepared.

We wish to report that we have confirmed that Kuru is an unique neurological condition well worthy of continued and intensive investigation. Undoubtedly it is a degenerative condition of the extrapyramidal system involving primarily

the basal ganglia but also probably the cerebellum as well.

The intensity of attack on the Fore people can be judged by the estimate that Kuru accounts for about half of the total deaths. If the nature of the disease could be discovered and its incidence controlled, it would be a magnificent achievement of medicine both in its scientific aspect and in helping these courageous and underprivileged people in the severity of their affliction. We feel that Australian Medical Science should be given the opportunity to co-operate effectively with the American workers that are already engaged on this investigation, and so to help peoples for whom we are responsible under the United Nations Charter.

We have been greatly impressed by the work that has already been done. There has been a systematic survey of the whole area of the Fore linguistic group and of the adjacent groups, some of which also have Kuru. The survey has extended beyond the furthest boundaries of the afflicted area. The clinical course and the uniqueness of the disease have been well established by investigations of several hundred patients. It has been shown that in the great majority of patients there is an inexorable progress of the disease to a fatal termination in 6-9 months. There is much information dealing with the peculiar age and sex incidence, and the possible familial incidence of the disease. Furthermore a wide variety of therapeutic agents has been tested, and an enormous amount of material has been secured, both from living and dead patients and despatched for examination, but as yet very few reports on this material have been available.

We wish to report that the investigations conducted by Drs. Zigas and Dr. Gajdusek are wholly admirable and worthy of the greatest praise. As yet the nature of the disease is unknown, but we would agree with the conclusion of Dr. Zigas and Dr. Gajdusek that it is very unlikely to be occurring as the aftermath of a viral infection. A number of possible causes of the

disease can be suggested, but these must be regarded merely as providing grounds for further investigation. Such investigations have already been initiated by the very thorough dietetic survey conducted by Miss Hamilton and by the large amount of material, such as blood, urine and brains that have already been despatched by Drs. Zigas and Gajdusek for trace metal estimations.

We further wish to report that it is necessary to continue the investigation intensively so that the magnificent work that has so far been done may be used to full advantage. It is urgently necessary to define the course of the disease by following up the known Kuru cases that are still alive and continuing with special therapeutic measures such as BAL and Versein medication. For example there are a few cases in which the advance of the disease has been checked, and it is very important to follow these cases closely and to watch for further exceptions to the inexorable progress. It is also essential to survey the area in detail in order to discover if there are subclinical cases and to detect new cases as early as possible, so that the clinical course of these cases may also be fully defined. Finally the range of the neurological signs of normal subjects needs to be investigated.

For these purposes it is essential to send an expert clinical team to be based on Moke so that a systematic survey can be made on the Fore peoples for a period of at least 8 weeks. It will further be necessary to provide adequate assistance for them. Dr. Robson, Professor of Medicine at Adelaide University, is prepared to lend this team, and to be available at the beginning of December, 1957. The estimated cost of this project is £3000.

NOVEMBER 7, 1957
[PORT MORESBY]

SMADEL
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND
USA

H3319 DESPATCHED LARGE SHIPMENT KURU TISSUES FOR TRACE
METAL STUDIES STOP AUSTRALIAN JOURNAL STILL AWAITING PHOTOS
STOP

GAJDUSEK

NOVEMBER 7, 1957
[NIH, BETHESDA, MD.]

DR. CARLETON GAJDUSEK
OKAPA PATROL POST
VIA KAINANTU
EASTERN HIGHLANDS
TERRITORY OF NEW GUINEA

ILLUSTRATIONS SENT TO MEDICAL JOURNAL OF AUSTRALIA NOVEMBER 6 STOP
EXTREMELY SORRY FOR DELAY STOP

JOSEPH SMADEL, M.D.

10 November 1957
[Kainantu, Eastern Highlands]

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland

Dear Joe,

Vin, Lucy Hamilton, Jack Baker and myself arrived in at Kainantu from Lae on a specially chartered plane this morning, flying up the long Markham Valley and climbing then into the more interesting highlands, once again, the Highlands in which I feel more "at home". We shall put out by jeep caravan for Okapa in a short while and I shall launch a brief final clinical follow-up study with some further evaluation of drugs...more BAL, testosterone and verseinate, I hope...and laboratory studies on as many patients as we can revisit and persuade to reenter our hospital. In 2-3 weeks I shall pull out, and on the 11th of December fly to Hollandia from Lae, bound homeward at long last.

I again reiterate, that I am in full accord with Visiting Investigator status at NIH if it will mean some salary soon upon my return; for a year without salary (I have managed to spend much more than the \$1000 grant from NFIP) is about enough, for I cannot swing it much longer. I will be back in the U.S. just after Christmas. From Hollandia and Biak I shall fly to Kuala Lumpur and remain there only a few days, instead of the months I had previously planned to spend there.

Kuru study must continue, and as I told you, an Adelaide group may (??) be able to keep up some sort of clinical follow-up pending my return to the scene in a year or so for a follow-up of my own.

I shall shortly get the records and files off for you to store with the Kuru file to which I hope to turn immediately upon my return to the U.S. The two trace metal-free brains now awaiting shipment to you are about hard enough and I shall get them off with Vin in the next few days after returning to Okapa. These are the last such specimens which will be forthcoming. There is some long bone and plenty of spinal cord with them! Thus, this may be the final neuropathological shipment on which you can count on for a while, and I beg that everything that can possibly be tried, be done.

Reports from CSIRO in Melbourne show traces of Cu and Al in most of the Kuru bloods and tissues studied and in some autopsy tissues. Mn was present in a few bloods and tissues and Zn in a few others. No other trace metals were identified by spectroscopic survey of ash for all elements and Mo, W, Zr, rare earths, and other rare possibilities failed to turn up. Of course it must be borne in mind that the special technique used might not be sensitive enough...there might be very little of an offending heavy metal atom in blood studied. Since Prof. Eccles agrees with us that only

trace metals are thus far known to give a picture anything like Kuru, we must still pursue this line. Cu levels on bloods have been completed at CSIRO by quantitative techniques and they, as the previously done Cu estimations at Port Moresby by the good agricultural trace metal lab have not revealed any elevations above expected normal. Blood alone was studied. Manganese, Aluminum, Zn, etc. have not yet been studied and these did show up in some specimens (Al in all!). However, Al-capped McCartney bottles with rubber washers were used and this may explain the finding and then again, Al is present in the highest levels of all "trace metals" in soils and in the field it is most difficult to assure total absence of any dust. We may be able to check back to see if any of the Al was found in specimens in vacuumatic venules as well as in Al-capped McCartney bottles...but I am not sure of being able to determine this. The cap, supposedly, does not come in contact with the contents, but?..?

From Moresby I shipped off to you the vast file of CSF, bloods, autopsy tissues etc. collected in specially prepared "trace metal free" containers or in standard venules. These should be used as whole blood, obviously, for long storage has hemolyzed them alot. They have been stored under refrigeration and should still be fine. Even if some are contaminated, they should still be OK for trace metal work.

From Kainantu we shall now mail off a large supply of toxic plants or plants suspected of toxicity which have been of particular interest in the Kuru region. Furthermore, we have a botanist coming to join us who will help make complete the huge taxonomic identification task--which is already nearly complete--of all the foods and medicinal plants of our Kuru-afflicted populaces. Many already appear to be from genera known to contain toxic species. Just how we shall sleuth out which, if any, might cause Kuru is hard to say. All efforts thus far have been to little avail. Kuru patients do not admit to using anything special or to being excessive consumers of any of the suspicious plants as far as we have been able to learn.

Kuru still "looks" like a solvable problem. As Eccles says, it is undoubtedly the most exciting thing in neurology in his whole long career in the field. That its "solution" may help with other neurological problems seems obvious. But, Kuru remains thus far unsolved.

The peculiar age-sex pattern leans me still toward genetic predisposition, at least, for in spite of criticism to the contrary, it is the type of thing genetic-predetermination can do. What of all the age-specific heredofamilial neurological degenerative disorders? And endocrine disorders? What of all the sex-specificity seen in such presumably genetically predisposed afflictions? This may be a different age curve and a more striking sex curve. But, Kuru is an undeniably unusual affair. However, we are still pushing the possibility of inapparent antecedent infection or thus far undetected deficiency or toxicity. No luck, however, as yet.

The botanical specimens going out are:

1. Agara (Fore) (also called Pinto)

Botanist identifies this as: Himantandraceae galbulimima Belgraveana. Big tree, growing wild in bush. Leaf and bark eaten to induce "dream man". Sometimes eaten with Ereriba (another Fore "drug"). Eaten after the evening meal. Eaten raw. Sometimes some is kept in the mouth during sleep. Eaten by women as well as by men, when they want insight into the future. Induces "skin guria" (Pidgen for kuru-like tremors) as does Ereriba. Not eaten by children. Fruit 'also is eaten raw to induce "dream man". Lucy believes that bark and fruit are eaten more than leaves, but leaves are said also to be effective. We are sending both bark and leaves of this plant.

2. Kegeta (Fore)

Botanist identifies this as Desmodium sp. (probably Desmodium sequax). Shrub 6 to 8 feet high. Grows wild in bush. Leaves eaten with pig and human flesh cooked in bamboo and mumu. (Cannibalism is almost gone, but not kuru). Found at edge of a Moke garden on 7/7/57. Bark chewed with bark of Obakoo, a tree, and Mapaia, a variety of sweet potato, and it is given to victims thought to be suffering from "Tukabu". Some is rubbed on the skin and the site of supposed "shutim nil" is then supposed to show up on the patient's skin. Many kuru patients (but not all, and not exclusively kuru victims either) claim to have used this plant. The leaves are eaten generally - by many kuru cases - and bark only used as a "tukabu medicine".

In Webb, L.J., "Guide to the Medicinal and Poisonous Plants of Queensland", Council for Scientific and Industrial Research, Commonwealth of Australia, 1948, we find:

Desmodium umbellatum DC. "Supposed by some to cause 'Chillagoe disease' of horses (Bailey 1909, 139)"

Desmodium nemorosum F. Muell. Reputed poisonous to stock (Bailey, 1909, 140).

Desmodium brachypodium A. Gray. A tick trefoil. This and Glycine tabicina were suspected of causing "string-halt" in horses near Stanthrope, April 1940 (Qld. Herb. Rec.).

Further pitpit samples have spoiled and Lucy will now start collecting new specimens. Ereriba leaves were sent off along with some rhizomes about 5-6 weeks ago and you should now have them.

A new possibility: Oenanthe javanica, consumed regularly by most Fore, is related to Oenanthe crocata, poisonous with spinal cord action on hind legs with paralysis. Oenanthotocis resembles cicutoxin (from Webb).

Also:

Iga (Igami)...a type of yam identified as Dioscoraceae discorea sp. Yam bearing aerial tubers. Aerial tubers and underground tubers eaten widely.

Webb states: several species of this genus with alkaloid dioscorine produces CNS action like pictrotoxin with paralyses.

Lucy finds that men use this more than women?...or at least they plant and care for it, but perhaps they feed it to women?

Vin has received your reply to his letter and is very pleased to be so promptly answered. He and Gloria, his wife, are taking 6 months leave from March onward and in June-July will cross the U.S. from Europe en route back to New Guinea. If any way to invite them to visit NIH etc. can be arranged it would be fine. I shall be there long before that and discuss this further with you.

TIME stopped in to get a Kuru-story while I was on the last "cross-the-island" patrol. Furthermore, in Moresby I was besieged by reporters--even equipped with tape recorders--and I am most disturbed and annoyed. "Laughing Death"...which is a hideous misnomer, fills most Australian papers and magazines with highly distorted and well-padded accounts. Vin saw the Australian TIME representative and seemed impressed by him and Vin expects a more balanced account from them. I am, however, skeptical and wish to Hell that Kuru were less a thing to fire popular imagination, for it will, I fear, be played for all it is worth by the press.

Please get a copy of the NEJM article off to me by air mail in order that I may see what appears. Also, Joe, please get the glossy prints off to the Australian journal (Medical Journal of Australia), for they must publish immediately being hounded as they are by the lay press.

Enclosed is a carbon copy of my letter of September 19th in which I asked for the 12 large glossy prints for the Medical Journal of Australia. In case loss or misplacement of the letter has contributed to the delay, this new copy--all I have--may help.

Also, enclosed is a carbon copy of the list of 8 developed but unprinted negatives I just mailed off to you. These should be printed, one copy each, in post-card size for the Kuru file in the NIH. They have much pertinent anthropological background material.

We shall now make further 16 mm cine films on Kuru. The 30 minute professionally photographed Kuru film (black and white and nothing spectacular in photography) was what I wanted it to be...a fairly detailed and all-inclusive account of the clinical picture of Kuru. I edited, spliced and rearranged it and then made, tape recorded and typed out a full sound track for it while in Moresby. It is off now to Canberra for a professional commentator and the Commonwealth Film Unit to work up the map, etc. and my text into a final product. Copies of the film (done in 35 mm but to be printed in 16 mm) will be sent off to you, as I have requested, and I hope to be carrying one with me, also, when I leave.

Eccles, Robson, and Sunderland all suggested my old Prof. Denny-Brown of Boston, as one of the world authorities on this type of illness, and strongly urged that we let him know all about Kuru soon. He may already have heard from you or others. If not, however, please Joe, will you inform him and see what he may have to offer? I hope to see him shortly when I am back home.

We have a host of world-repute entomologists at work in New Guinea at the moment and three have already been out to Moke briefly to see Kuru. They have identified or are identifying the "food" insects and larvae and we talked them into collecting the kunai-thatch-investing rodents (two species of the genus Ratus, I am told) and into combing the rats for mites (which are very plentiful), fleas, et. and in hunting out other ectoparasites. I do not have their taxonomic results as yet. It will be worth having, however, although thus far I cannot get excited about infectious possibilities.

The Fore houses, as all Highland native houses, are smoke-filled. However, it has recently come to my attention that the Fore women and children, especially, may be particularly exposed to a perpetual smoke-filled atmosphere (women's houses are smaller than men's and have no vent-hole). Thus I shall soon get more ash specimens off to you from Kuru victims' houses along with controls. What to do with them is a problem, but it is certainly worth knowing whether they are unusually rich in Mn, W, Pb, Zn or some such metal.

I shall get the cine camera shipped back to the NIH just prior to my departure from the Kuru region. Thank you again for all the support and thank everyone at NINDB also, for me.

Sincerely,

/s/ Carleton

NOVEMBER 11, 1957
[OKAPA, TNG]

SMADEL
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND

PLEASE SELECT AND PRINT TWELVE NEW KURU PHOTOGRAPHS FROM ALL
AVAILABLE NEGATIVES FOR ARTICLE STOP SHIPPING TWO TRACE METAL
FREE BRAINS STOP

GAJDUSEK

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
November 14, 1957

Dr. Joseph E. Smadel, Associate Director
National Institutes of Health
Bethesda, Maryland
USA

Dear Joe,

The enclosed two letters to be added to the Kuru files will tell you a bit more of what is going on. Actually, there are a dozen further studies of every sort I am trying to correlate and organize and the entire job is fantastically immense. Coupled with the current attempt to reevaluate every living Kuru case during the next two weeks before I leave and to collect the last batch of specimens, the correspondence and paper revision and correlation work has me working from dawn to dawn.

Vin apparently did not realize the absolute necessity of NOT letting press and newsmen see papers in print and the politics-ridden Port Moresby administrative office also broke faith and released on every hand data I had given them in Confidential and Restricted manuscripts which were in press and I found myself, upon emerging from the Papuan jungles and swamps after almost 2 months of patrolling, surrounded by radio and press men and their "Laughing Death". To my horror, however, it appears that the local TIME reporter, visiting the Post in my absence, got his hands on personal letter files and all manuscripts--finished and in preparation--and although I have not yet seen TIME's accounts, I warn you to expect anything and everything, for no one here has the slightest idea of the usual and ethical channels of scientific publication. I would not be surprised to see the restricted clinical film I have just prepared, directed, edited and scripted and sent off to Canberra for final printing, advertised in sensational large print in the Cinema ads in the Sydney Herald. These, then, Joe, are the odds under which I am now working. Sorry for it all...but what the Hell can one do from the unexplored Kukukuku mountains in which I have been at work.

Everyone here is more interested in TIME, LIFE and Australian press accounts than in the careful investigation and elucidation of the disease and as one emerges from these protected Highland outposts to Kuru-free regions politics and National and individual pride take precedence over accurate analysis of data and cautious study of the problem.

In spite of it all, however, we may be able to get a good deal more done in the next two weeks. Lucy Hamilton is back with me and we have sent off with the two trace metal-free brains and visceral tissues on two Kuru cases, a stack of pitpit of the two alkaloid-containing varieties you requested. Already en route to you are stacks of specimens for toxicological study. The Erereba trials I would take with a grain of salt, but in the next week I shall make new trials of it and send on reports.

One bottle of fixed visceral specimens is in trace metal-free formol saline and thus may be used as such. Zenkers fixed specimens are in 70% C_2H_5OH as usual. For Atona we are sending a good long piece of spinal cord and a good section of long bone also fixed in trace metal-free formaldehyde. Please cable me whether the first trace metal-free brain which you have already received was adequate for neurohistology as well. Very restricted quantities of trace metal-free formaldehyde have made fixing in very small volumes of formaldehyde necessary, and I am worried. The long bone section may be the only one we shall get. Sorry they did not get it more distally or proximally for the epiphyses.

Cable any further suggestions or results which may give us any ideas, for we are winding up the field program in the early days of December. Also, list your cable address in your next letter or cable. I am wasting a fortune in the long address at international cable rates.

Botanical check lists of all Fore diet and contact plants are being typed and will soon be off to you for distribution to toxicologists, botanists, and pharmacologists for suggestions. I will also send off such staples as kaukau (sweet potato), yams, etc. for trace metal analyses along with fire ashes from Kuru houses for similar studies. Smoke from these fires may be important. Geologists tell me there is much arsenical iron pyrite hereabout and whether this might get into food from the "mumuing" of food by steam-cooking in pits using hot stones or in some other way I do not know. Arsenic analyses are thus in order, although what little I know of it as poisoning, has not led me to suspect it at all in Kuru. Of course some organic arsenical might act quite differently.

It seems rather certain that Kuru progresses from early or moderate stages to fatal termination even in patients removed from the native village to our Kuru Center and here almost all the "exotic" foods such as grubs, fungi, wild fruits, grasses, herbs, etc. are no longer components of the diet and even smoke exposure is minimal. They do still get a good deal of local garden staples--but a good deal of rice and canned meat supplement. Cases removed completely from the Kuru area to Kainantu (and the case I dug up from history in Lufa) seem also to progress out of the Kuru setting. Although this is not a conclusively proved matter as yet, it certainly must influence our thinking along possible toxic lines. A poison which produces a hardly perceptible initial lesion and for which the lesion progresses even when further contact with the agent is impossible must be considered. These are few as far as I know.

Has histology of other organs given any clue?

I have cabled you requesting selection of another dozen good clinical and epidemiological pictures from the Kuru file for the German article. If large glossy prints of these can be sent off to Klinische Wochenschrift and small copies to me so that I may prepare captions, I shall be most grateful. The German paper will be the most definitive and elaborate of our three and I do not plan to work up any more of our data until I get to see you in Washington.

Enough for now. I have been at the typewriter for 24 hours with only a few breaks to organize the "rerounding-up" of our Kuru patients and to visit those I have in the hospital. If it were not for the wonderful fun I have with these marvelous natives for whom I hope we may eventually bring some relief to their affliction, the bastards on the periphery of our problem would drive me from it. I am impatient and in a bad mood, excuse me.

Sincerely,

/s/ Carleton

Carleton

P.S. Another postmortem at 6 a.m. this morning with all organs, sciatic nerve, brain, testes, adrenals, and all other viscera taken. Brain is in trace metal-free formol saline, but we have used the last such in the Territory and it is hardly in two volumes of the fixative. It is for this reason that I want to know if the first brain was well fixed (i.e. trace metal-free) for we do not have 5-6 brain volumes of trace metal-free formol saline to use. We are, at the moment, out of all formaldehyde and fixative, but I hope some comes in to Kainantu from Lae by plane today and we will have it here, with luck, tomorrow. If we have any deaths in the next 24 hours--and our patients have been dying almost daily now--we shall not be able to fix tissues. Thereafter all will be OK again. At the moment I have no Wrights or Leischman's stain and unless a plane gets through from Moresby with it soon, I cannot do any further blood smears. These are just the usual problems, but when I come back I hope it is with all these solved.

Carleton

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
November 12, 1957

Dear Roy,

It takes a lot of courage to write to you, having involved you in one of the all-time classical blunders of scientific investigation. I set out on the six weeks Kukukuku patrol carrying ample venules and your glucose tubes ready to bleed the Kuks galore. However, the rugged country and time-consuming trip to reach them proved that there was no possibility of getting out of the Kuk regions into which we had penetrated any specimens short of long unrefrigerated carriage. I abandoned the idea.

However, before leaving on the patrol I had alerted our very good European Medical Assistant, who has been assisting in our program here at Okapa, to my plan to rush back non-stop overland the specimens, and he was fully briefed on how to pack them into plastic bags, into the thermoses, and to wire immediately for Jeep transport to Kainantu to be rushed in and he and Dr. Zigas were ready to keep all refrigerated until it was finally placed in ice on the plane bound for Melbourne. All just as planned. However, I changed my plans, and after ending up our major Kukukuku work, I came to the Lamari shores poised ready for a gamble at returning to the Yar people to the south and crossing the entire island down to the Purari and descending it to the Papuan coast. This plan demanded lightening our cargo. Thus, a large portion of our supplies and many of our cargo boys were sent slowly back to Moke-Pintogori (i.e. the Okapa Patrol Post) with letters explaining to John Berkin and Vin Zigas (John is our EMA) my plans and asking them to attend to numerous things. However, I made no mention of the unused glucose tubes I was returning for eventual uses later. Instead, I had packed them into the bottom of one cargo box, unopened, empty, and, since all was going by a leisurely overland route without any note from me explaining who had been bled or where, I never dreamed of the possibility that in zealous following of directions the empty returned tubes could have been found and interpreted as collected specimens, as was done. Thus, John did exactly as I had instructed him and packed them all off and rushed them to you. It is only now that I am back and looking for them that I have become aware of what has happened. In Moresby, for we did succeed in reaching the coast, Vin appeared at the Kuru meeting we had there and I told him of my plans and arrangements to have a large group of our Kukukuku friends come in to Okapa and be bled directly adjacent to our ice-boxes, thus avoiding all the dangers of long delay in overland, unrefrigerated transport. Then he told me that the specimens had been sent out in good order and I almost collapsed.

If, Roy, you have convalesced from your hospital sojourn after the heart attack I assumed you suffered on opening 300 empty tubes, I hope you will be willing to read on:

To your letter of 14-10-57:

With these reports all specimens we have sent to you and of which we have records are now recorded and it appears that we are very close to being able to sit down and make really valid analyses and evaluations of the data. In spite of the overwhelming conviction that some hidden toxin is lurking behind the Kuru-story, the genetic predisposition or full determination probability remains unshaken and thus far the most likely... although even I myself am somewhat skeptical. Our patients are dying on every hand and the entire problem is more spectacular as time progresses. Unfortunately, newspapers have gotten hold of our story and all data on Kuru--which ultimately must stem from Vin or myself since no one has seen anything of it other than what we have revealed or shown to the few who have visited--and a brief view thereof by anthropologists Berndt and wife in 1953--all data on Kuru is being printed in a most distorted and completely misleading fashion. Even direct quotes from our letters and reports appear in press in much distorted version and our own statements are misquoted. However, the Nov. 14 issue of the New England Journal of Medicine should have our first preliminary report in it. At the moment I am in a telegraph battle with the editor of the Medical Journal of Australia who is trying to rush into print with our second paper on November 28th before making the essential alterations and corrections in the original manuscript without which the Australian article will be inaccurate, incorrect, not up to date, and very misleading. I hope I can hold his presses long enough for him to make the changes which are already posted in the mails to him. If not, I shall certainly refuse to publish another one of the many further Kuru studies which we already have data for in the Australian journal. There is absolutely no difficulty in getting our Kuru papers printed anywhere we wish and in a great hurry. That being the case, I am very annoyed with the rush precipitated upon us for hurried publication by editors and politicians involved. If they will wait long enough to get the corrections and additions--the Australian paper as is does not even have the neuropathology reported which we have fully described in the NEJM paper, and that at least must be added if it is to be any better than the newspaper accounts--I shall be most happy. If they jump the gun on me and publish before I have seen galley proofs, I shall be most disturbed. After all it is our paper and if we do not care about delay in publication and if we insist on seeing proofs before publication, I think we should have that right. Otherwise I shall be forced to retract much that appears in Australian accounts on Kuru. Sorry to inflict all this upon you, Roy, but the latest telegrams have me worked up.

To get back to your blood group studies. I am enclosing sheets which should straighten all this out and bring all specimens you have studied to full documentation and proper assignment to groups. Here is the score:

Lot 12 - Specimens Nos. 117-131 inclusive. Just as you record them and properly assigned to Fore or Kukukuku Surveys by the information on the lists.

Lot 13 - 41 specimens in a confused group which are sorted out and completely documented on the enclosed sheets. The Yar people specimens which you list on one sheet as "not received" are included in this group and I have indicated which specimens they are. These Yar results should be grouped with Yar results from Lot 15.

Lot 14 - 87 Kimi blood specimens of which you have had to discard 9 specimens, and 78 specimens have thus been studied. All Kimi people.
Incidentally, Moseiena F-30 is a case of so-called "recovered Kuru" from the Kimi people. Keep her aside and do not include her with typical Kurus. Her blood specimen arrived along with these other Kimi specimens.

Lot 15 - You have had to discard the following 8 specimens: (F95, F106, F8, F29, F38, F55, F79, and F18)

The remaining 100 specimens consist of:

98 Fore people

2 Yar people (Numbers F107, F108)

(incidentally, in the tribal-designations on the two sheets which document these specimens and the ethnic background, the Kimi tribe is a Fore People tribe, and not the Kimi People or Kimi Linguistic Group which is a different race bearing the same name. The specimens of Lot 14 belonged to this Kimi people (Linguistic Group).

In addition, with Lot 15 you list:

Aurika

Esita

Both are Kuru patients as you have recorded them.

Also: Kaikai M/20

Maiai M/20...should be Maiari

Wapi M18

These three are Yar people to be included with other Yars in Lot 13 and specimens F107 and F108

Finally: Anna 5/9/57 This specimen I cannot place and I shall start tracking it down. Will write about it in a later letter.

Lot 16 - Cargo Boy Series.

I shall send you documenting sheets on this series with this letter. See enclosures.

Here, then, is full documentation of everything you have thus far received.

I am sending by refrigerated air shipment several further specimens. These include several on Kukukukus who have walked into our Patrol Post as I arranged that they should and they have just been bled here and their blood specimens refrigerated promptly. Also, other interesting specimens to be included in the Kuru and also the Non-kuru files are included. All are fully documented on the enclosed sheets and their numbering starts with NO. 132. Thus, with these I am going on from the bleedings of 22 August 1957--(included completely in your Lot 12)--and continuing serially. As in the 117-131 series, the sheet makes Tribal assignment clear.

Finally, Roy, under Lot 16 on the previous page I referred you to "see enclosure". Now it becomes evident that I typed a list of the Cargo Boys for the Kukukuku patrol on 26 September just before leaving and I assume that this list was mailed to you along with the specimens. It contained full documentation of the CB-1 to CB-44 series with place of birth of Mother and Father and cultural and linguistic group of each subject. Thus, I believe I do not need to retype this list now. If, by any chance, you do not have this list in which the various specimens are assigned to appropriate Keiagana, Kamano, Fore, Iagaria, etc. linguistic groups, please let me know promptly and I shall send one on.

In a short while I hope to get off to you the final series of Kuru bleedings. Lois will take the sterile sera on these and ship them off to the Kuru file in the USA where I shall work on them, if you will be willing to get these to her. Aliquots should go to Cyril Curtain for his work and, if Dr. G.N. Cooper, Chief Bacteriologist of Public Health Laboratory of the University of Melbourne could be given specimens of the Kuru blood sera for streptococcal agglutination studies he is doing--Lois will get these off from the specimens you give her--that will take care of all we have in mind. Cyril Curtain may be willing to take clots for further hemoglobin search. In addition, during these final 2-3 weeks of our field project....after that Roy, there will be no further specimens....we shall try to bring the number of adult normal subjects of racially pure stock from each of the Kuru area and surrounding racial groups (cultural-linguistic groups would be better) in your file to about 100. I shall not collect indiscriminately, and everything collected will be aimed at bringing to final statistically adequate sampling each group you are now studying and as I send specimens, I shall document them fully.

My address, once I leave here, will be

Dr. Carleton Gajdusek
c/o Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland
USA.

I must pass across Asia and Europe en route home, but in about 1-2 months from the time I finally let you know I am leaving the territory I should be there at work on Kuru once again with all the files, notes and data in my hands. I shall then be doing lab investigative work on Kuru specimens and planning for a new 1958 field attack on the disease and making full analysis of the immense stacks of data for definitive publications on Kuru. From there I can do all the correlations and writing necessary in collaboration with you to get the Kuru and Kuru area blood group genetic survey worked up. I shall also have all the cartographic material on hand for a series of extensive ethno-cultural maps to go along with the Kuru-region large scale maps we shall be preparing. Thus, Roy, please accept my assurance that you will not be left "holding the bag" as much as you were with the Cape York and the New Britain data.

My apologies again for the "impossible" error in the shipping of the glucose tubes. Let me know how things work out. You can still reach me here until the first days of December.

Sincerely,

Carleton Gajdusek

BLEEDINGS DONE 13 November 1957 AT OKAPA PATROL POST

<u>No.</u>	<u>Name</u>	<u>Sex-Age</u>	<u>Tribal-Linguistic Group</u>	<u>Village</u>
132.	AWANTI, Tultul	M-30	AWA	Agamusei
133.	KIVINAGA, Luluai	M-35	KUKUKUKU	Uraba-Auroga
134.	YAMONTAWA	M-28	KUKUKUKU	Uraba-Auroga
135.	NABARAKOI	M-25	KUKUKUKU	Uraba-Auroga
136.	CHOGOIME	M-20	KUKUKUKU	Uraba-Auroga
137.	KUMBURIYANI	M-25	KUKUKUKU	Uraba-Auroga
138.	INDOVARINA	M-25	KUKUKUKU	Uraba-Auroga
139.	AVIARACHE	M-25	KUKUKUKU	Uraba-Auroga
140.	KAGEINARO	M-9	FORE	Agakamatasa
141.	UWARA	M-9	FORE	Agakamatasa

Blood specimens for blood group genetic and abnormal hemoglobin studies and save serum for serological epidemiology and serum protein studies. All pureblooded members of respective linguistic groups who are well and healthy.

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
November 13, 1957

Dr. Cyril Curtain
Baker Institute
Alfred Hospital Clinical Research Unit
Melbourne, Australia

Dear Cyril,

I am late in answering your letter of September 27th and I have much to say. Roy Simmons continues to get shipments of blood specimens from Kuru cases and non-Kurus and he can continue to supply you with every sort of serum you may desire. However, it is in your work as in his essential that your specimens be accurately and exactly correlated with the phase and stage of illness in Kuru sera and at least with the individual and his ethnic location for the controls. To do this I must check the names on the lists of results you have sent me against my records. We have extensive charts on all patients and complete records on all specimens we sent out. Controls are also documented as to age, sex, state of health, date of bleeding and ethnic group, village of residence, etc. It is, obviously, high time to make certain that those specimens you are studying are correctly grouped. It is in an attempt to do this for you that I now write. Also, Cyril, I must express my appreciation and thanks to you once again for your help and cooperation in this most intriguing problem. As you have no doubt seen, we have been plagued by reporters and newsmen and radio men on every side and I am furious, helplessly at their mercy and most disturbed. It would not be so bad if radio and news reports were inaccurate, misleading, far-fetched and sensational and ridiculous--for what else does one expect of them? But, from them it is obvious that much of our correspondence and, what is worse, manuscripts of our preliminary reports now in press have leaked out to newsmen. Finally, in an attempt to preserve the Medical Journal of Australia from the embarrassment of publishing an outdated, already superseded and somewhat inaccurate account, I am now having a running telegraphic battle with the editor, trying to convince him of the need for withholding publication until the much amplified, revised and corrected manuscript now in the mail en route to him is received. Politics, national pride, personalities--all of which have nothing to do with the study and investigation of this dread affliction of these fine native people--are forcing the editor's hand, and if I lose out in getting a well proof-read, edited and corrected paper in the Australian press simply because of their politic-national-pride panic, I shall never publish a word further of this kuru story as it unfolds in the Australian journals. Now, to the work of this letter, if I can cool off enough.

First: The list of corrected names of the first series of sera are:

Ailaia, probably not Kuru; is well now.
Aranaka, died of Kuru.
Ereio, died of Kuru.
Inare, dying of Kuru; terminal now.
Kako, not Kuru.
Manto, died of Kuru.
Natameia, died of Kuru.

Even on your corrected list, you had Ailaia listed as Alaia, and Aranaka listed as Arankaka; and Natameia listed as Napameia...please correct your records accordingly.

Second: The sera you refer to as "first series" I do not place. In your letter of May 23, 1957 you sent a stack of patterns on graph paper, along with some paper electrophoresis strips. I assume all those listed above. However, there are still some problems. In your first set of results, one was listed as Aila and that I assumed to be Ailaia. Now you state that Niaia (on your list) is Ailaia. Can you straighten this one out? I have your charts from the "first series" on:

Ailaia (which one, Naiaia or Aila?)	
Aranaka	Aso
Ereio	Mulinapa
Inare	Inome
Kako	Asomeia
Manto	Kinao

However, I received none on Natameia and you have her listed on the sheet of corrected names. Were there any others in this series? I still have graphs on:

Lakuo
Faruou 5/5/57

which are two names I am totally unable to place. Can you straighten these out?

Third: Your first page of results in this last letter is herewith documented:

<u>Your listing</u>	<u>Correct name</u>	<u>Remarks</u>
Haimara		I cannot identify this patient; please check name and date.
Intakoz 8/5	Intako	Died of Kuru
Ia'i 30/5	Ia'i	Died of Kuru
Yaknoa 24/3	Yakona	Probably not Kuru
Iamogi 7/6	Iamogi	Died of Kuru
Kagobina 7/6	Kagobina	Died of Kuru
Kairosafina	Kairosafina	Died of Kuru
Kaiao 30/5	Kaiao	Severe Kuru
Waranesa	Waronesa	Kuru
Abarerri	Abareri	Kuru
Utavuna	Utavuna	Kuru
Vidumu	I'Idumu	Kuru

Thus, of these twelve specimens, five are from typical kuru since deceased. Five others are from Kuru cases still surviving. One is probably not a Kuru case and should not be included with results, and one I cannot identify at all from the name you supply. For all of them it would be worth getting the date of venepuncture from Simmons' records for stage of illness may influence results markedly.

Fourth: To make a similar survey of another of your sheets reporting results:

Omaiyo	Omaiyo	Probably not Kuru
Amuraissa	- the name of a place, not a patient; can you recheck for patient's name on label?	
Taranto 25/5	Taranto	Dying of kuru
Lyarabo	Iyarabo	Kuru
Tekeiaya	Tereiavi	Died of Kuru
Tvoga	- I cannot identify this name; please recheck.	
Aveto 25/5	Aveto	Kuru
Noka 30/5	Noka	Kuru
Asisi	Asisi	Dying of Kuru
Meio	Meio	Died of Kuru
Tete	Tete	Kuru
Atogori	Atogori	Kuru
Faia	Faia	Died of Kuru
Wawasi)		
Are'u)	This group of five specimens I cannot identify at	
Evesia)	the moment. They are not Kuru cases. Please send	
Pegare)	me any further information on them you can, such as	
Toya)	dates of collection, receipt and what shipment (?to Lois, or to Roy)	

Thus, only eleven of this group can definitely be included in the Kuru series. Eight cannot be identified. Finally, you sent two sheets stapled together with results on them of 33 serum specimens. Some of these are not Kuru cases; thus, I summarize these:

<u>Your name</u>	<u>Correct name</u>	<u>Remarks</u>
Aso 24/3		Died of Kuru
Nene 28/5		Died of Kuru
Kagobina		Died of Kuru
Mer'eimama	Mer'ainamu	Atypical Kuru (?)
Ereio		Died of Kuru
Inam		Died of Kuru
Iamu		Died of Kuru
Namabufa	Namaorufa	Died of Kuru
Intako 28/5		Died of Kuru
Haimara	- unidentifiable - please check this name and specimen	
Tabubi	Tatubi	Died of Kuru
Yobaioto 28/5		Died of Kuru
Ailaia 24//3		Probably not Kuru
Kako 24/3		Definitely not Kuru
Asomeia 24/3		Died of Kuru
Kagobina 28/5		Died of Kuru
Inare 24/3		Dying of Kuru
Manto 24/3		Dying of Kuru
Fopota 24/3		Probably not Kuru (?hysteria)
Ereio 24/3		Died of Kuru
Nogunta 24/3		Died of Kuru
Inome 24/3		Died of Kuru
Arankaka 24/3	Aranaka	Died of Kuru
Mara 24/3		Not Kuru

Kinao 24/3		Died of Kuru
Ivuti		Not Kuru
Mulinapa 24/3		Died of Kuru
Yoiea	Yoeia	Died of Kuru
Gotu 28/5		Kuru
Aoga 28/5		Kuru
Aoga 24/3		Kuru
Amakiora 28/5		Probably not Kuru

Thus, Cyril, these listings should serve to help you arrange the data into appropriate groups. When I list "Kuru", rather than "Died of Kuru", I mean to imply a typical case which is still surviving and probably will die shortly. All problems such as those I cannot identify require checking against original labels, Simmons' or Lois' records, etc. If you rush this information to me I shall probably be able to straighten everything out before early December when I plan to leave for the U.S., to go on with kuru lab work there and the preparation for another intensified field-laboratory approach next year. I am most interested in learning what develops in this study of serum proteins. However, I must reiterate the need, which you fully appreciate, of further and further controls. This is so because a great deal of study already has indicated most unusual serum protein patterns in New Guinea natives. We did a series of New Britain sera last year with Zara Wheaton at the Hall Institute, and everyone showed enormous gamma globulin elevation and paper electrophoresis was most remarkable. I know that Bill Smythe in Rabaul has been finding greatly elevated globulins by paper electrophoresis and precipitation tests (crude as they are) in most New Britain natives. The Western Highlands group is rather dormant now, I believe, but I do know that Walsh did have some highland globulin data and I was told that there again "abnormal" globulin patterns did appear. Now, there is nothing I should like better than a good lab-lead on Kuru, and the possibility that your results are on the track is the most exciting possibility yet turned up in Kuru, Cyril. However, please complete tables based on the case identification I am herewith providing, and let me document carefully all of your "controls". Thereafter, if you get to me the revised, regrouped data when you can eventually get it compiled, I shall very promptly make correlations and breakdowns within each group by age, sex, stage of disease, etc., and we can even spot such things as malaria-affected populaces with spleens, etc. (some portions of this region are malarious), and malarial-free populaces. The supply of "normals" should be fairly adequate, for I have been sending rather large Fore, Kimi and other local tribal group blood collections to Roy Simmons.

It should be borne in mind that whenever the names of Kuru cases are identical, the specimens are different bleedings on the same patient and these should be grouped together in chronological sequence in making up your tables. If you can find the time, I would very much like to see what further results have turned up to get further data on the specimens you have already reported, which I have been unable to identify, and to see your control data with all the information on names, numbers, lots, etc. of these "controls", so that I can document them properly for you. It is possible that age, sex, invalidism and other non-Kuru variables are involved and it is for this reason that I urge you to get the specimens all properly catalogued as soon as possible. Please settle on the definitive spellings, as I have indicated them. It is an immense problem locating misspelled names, and often an impossible one. We have so many different "series" of studies and specimen collection under way that numerical designation systems have not always been used.

For the Kuru cases we have restricted ourselves to a single definitive name for each case, and if the spelling is not in error, our alphabetical file serves to locate cases for us promptly.

I shall shortly be sending to Melbourne, either to Roy or to Lois, new bleedings on several dozen Kuru cases. These will be the final bleedings before the Kuru study is temporarily discontinued, and it may be very difficult to get any more specimens from the field until we get the new, renewed field project organized, which may be a matter of months, perhaps a year. Thus, send your requests for specimens promptly and stand by for portions of whatever I send down to Roy and Lois. Please tell Roy, however, that some of every serum specimen must be saved for serological studies we hope to carry out on the specimens. Should you have any ideas of anything else to track down in the sera, please follow through every "hunch", for the specimens will be refrigerated and fairly fresh and we need every lead we can get.

Again, Cyril, my thanks. After mid-December you had best address me in the U.S. I shall send you my mailing address and dates in my next letter. For the moment, however, I hope to hear from you again while I am still here in Okapa.

Sincerely,

/S/

Carleton Gajdusek

Okapa Patrol Post, via Kainantu,
Eastern Highlands, Territory of
Papua and New Guinea

November 13, 1957

Dr. E. Graeme Robertson
Department of Neurology
and Neurosurgery
The Royal Melbourne Hospital
Melbourne, Australia

Dear Dr. Robertson,

I thank you for your letter of September 23rd. I left on an extensive patrol around the border of the Fore kuru region, through uncontrolled Kukukuku country, and eventually crossed the highlands and descended the Lamari, Subu and Purari Rivers to the Papuan coast on September 26 and, thus, did not receive your letter until I arrived in Moresby on November 3rd. I am most sorry not to have been on hand to know of your pathological findings earlier. The report of the 16th August never was forwarded to me by any who may have seen it, and the report as I now see it would have influenced my thinking considerably. In the meanwhile, our American collaborators (at the National Institute of Neurological Diseases and Blindness of the National Institutes of Health) had cabled to me a report of more extensive neuronal degeneration, especially in the cerebellum, as you report, and also in basal ganglia, anterior horn cells, inferior olives, thalamus and pontine nuclei. The neuronal degeneration in the cerebellum and extrapyramidal system, they say, is associated with extensive neuronophagia. KINAO, the first patient whose brain we obtained and sent to Melbourne, was a very typical case of kuru. However, our fixation may have been at fault and we had originally been requested by the Hall Institute group to cut the brain into slices before fixing. Subsequently, both you and the U.S. groups requested fixation of the unsectioned brain...that is what we have now been doing. Two further brains were sent to Melbourne and from your letter I see that at least two are in your hands. Did the third case reach you; can you identify the cases by name? Case I is KINAO, undoubtedly; which of the two subsequent brains is identified as Case II, I do not know.

We are most disturbed by the dreadful publicity kuru and our work is getting in the press and radio, and extremely annoyed that our "Confidential and Restricted" manuscripts in press, with the medical journals, have been shown to the press here in the Territory. Our first report is out, I believe, in the New England Journal of Medicine; our second report should soon be out in the Medical Journal of Australia. Unfortunately, I am now having a telegraphic battle with the editor of the Australian journal, trying to insist that he NOT rush to press before I have corrected galley proofs, and before the essential additions and corrections are made to the article in his hands. Without them, it will be a most inadequate and incomplete report, and of no credit to the journal, and hardly up to some of the lay press accounts. With the corrections I have already in the mail to him, the paper will be a substantial contribution to the kuru problem. However, he has informed me today by cable that he cannot wait for our corrections. Since I have not yet even seen proofs, I am understandably furious, and if the paper appears without the minor alterations and

without my having seen galley proofs, I shall not easily forgive the journal its needless haste.

Vin Zigas and I are trying to wind up now our nine months of kuru study, in order to settle down and evaluate our immense stack of clinical and laboratory records and to plan with the aid of our laboratory collaborators a renewed field approach to the problem for 1958, during which I plan to return to the Territory for a further attack on kuru. I shall keep in close touch with you, Dr. Robertson, and shall await further word as to what you have found on neurohistological study. I shall also keep you informed of what the American workers report on the specimens they are studying. When we re-assemble patients again from their distant and scattered hamlets, when the kuru field project is again opened--for as I have said, we are now "closing down"--I certainly hope that you can visit our Kuru Research Center and help us with this fascinating problem, in which your pathological investigations are already of great assistance. I thank you for your interest and cooperation.

Sincerely yours,

D. Carleton Gajdusek, M.D.

Okapa Patrol Post
via Kainantu, E.H.
Territory of New Guinea
November 15, 1957

Ronald M. Winton, Editor
Medical Journal of Australia
Sydney
Australia

Dear Dr. Winton:

Enclosed you will find the fully corrected galley proofs which we have immediately corrected and rushed back to you. If your printers follow corrections on them carefully, we shall be fully satisfied with the article. The enclosed manuscript is a retyping of the corrected carbon copy of the original manuscript which I rushed off to you a few days ago and on which I have now made those grammatical, form and word-order corrections which I find you have made in editing the manuscript. Thus, this manuscript should correspond exactly to the galley proofs and can be used for rapid reproof-reading of the printer's corrected galley proofs and page proofs.

We have just cabled you as follows:

CORRECTED GALLEY PROOFS MAILED TODAY STOP WE MUST REFUSE
PERMISSION FOR PUBLICATION WITHOUT THESE CORRECTIONS STOP
PLEASE DO NOT JEOPARDIZE SCIENTIFIC ACCURACY FOR SAKE OF
PANICKED RUSH TO PRINT STOP GAJDUSEK ZIGAS

I am sorry that we have had to be so insistent. As it stands, your galley reached Kainantu on November 14th yesterday, and thus, your note requesting corrections by mail by November 13 could not possibly be observed and cable of proof corrections, even if minor, would have been inconceivable. We have not held up the proofs having returned them to you in less than 24 hours of their receipt by us. We must insist on these corrections if the article to appear in your journal is to be a worthwhile scientific publication. As it is, the first preliminary report which has appeared in the New England Journal of Medicine has had incorporated into it the recently obtained dramatic neuropathological findings and the changes in attitude resulting from these. To our dismay our "restricted and confidential" manuscripts have had material from them released in Port Moresby to newsmen and we find the ridiculous and disturbing reports in the lay press contain mention of case numbers and pathological findings and hypotheses which would be more accurate and more up to date than the report would contain in your journal, if it appeared uncorrected. What would make matters worse, we should be forced to immediately revise and restate our results and conclusions in articles in other journals IF the original

article remains uncorrected. I was expecting time for a slow, leisurely correction of the galley proofs and thus had set the pathological findings aside for inclusions when the proofs arrived. I then noted that they were based on study of autopsy specimens obtained from a larger series of cases than those summarized in the text as it was first prepared, and therefore took the opportunity to revise the case series to the 154 level at which important changes in our view of the age-sex incidence pattern began to be evident. This is the background for the revisions. They do not demand any extensive breaking up of type. Instead, they demand only cautious correction of all existing type and deletion of only a few sentences in the entire proofs. In place of these deletions a few new texts, a bit amplified, are to be inserted.

Since your journal has been willing to publish as long and extensive an account of Kuru with ample illustrations it is certainly fitting that it be a medically and scientifically sound and up to date report. To have it lagging behind, and inaccurately at that, the hideous accounts in the lay press and to have it contain material which we must immediately modify, retract, and correct in articles in other journals certainly reflects poorly on the article as published and the journal in which it appears. For these reasons, Dr. Winton, Dr. Zigas and I are adamant in insisting that time be taken to see and follow out proof corrections. If you and your editors follow the printer's corrections of the type, Dr. Zigas and I shall be willing to leave in your hands the final rereading of the galley and page proofs and we shall be satisfied with your checking of the map, illustrations and appropriate number of the captions for these. Please be certain that the photographs you received correspond to those which I selected and that captions are appropriate.

We thank you for this difficult matter of editing and for the added effort our corrections impose upon you. If the paper appears with the proof corrections observed we shall be most anxious and willing to publish some of the further reports on Kuru which are in preparation with your journal, should they meet with your editorial approval.

Sincerely,

D. Carleton Gajdusek, M.D.

November 16, 1957
Okapa Patrol Post

Dear Joe,

Enclosed is a letter to Sir Mac on the second page of which is an item, marked in red ink, which you and others should know about. Yes, this is really a distinct new non-congenital and progressive CNS syndrome known to the people of the Kawaina-Nambaira regions by the name Tukeseina or Tukesia, and which runs a course moderately different from kuru--we even spotted the difference ourselves in the stance, tremor and gait--and of which we now have one patient. I shall soon study him intensively and take motion pictures of him. The course runs over several years, tremor is more constant and regular, gait and stance are impaired in a different way than in kuru. We have really not studied it well yet. The people affected are just beyond the kuru border in an "uncontrolled" region where they still shoot arrows at us, and they have a full tradition of the disease; we shall look into it further.

An Adelaide University team will arrive to carry on clinical follow-up of our cases in mid-December. We are, at the moment, entirely on our own, however, as we always are in this study except when it comes to talk in Moresby, and we are trying to do an immense job in the next few weeks. Please let me know what you think of the possibility of getting NIH help for a return expedition in under one year if I get back shortly. I must return and shall return...but I would rather do so on an income with some support. Is there enough interest in kuru and the associated problem to make it likely that if I get to work on it back in the lab, I can escape for a brief follow-up study before the end of 1958? I am making plans for that here as I prepare to leave.

Enclosed are a few odd case-record copies to simply be put in the kuru record file. However, shortly I shall be shipping immense piles of case records, correspondence files, etc. Please, Joe, keep your eyes on them, for all of our results are incorporated in these files of case records and correspondence and it is on these that I hope to work immediately upon my return.

Sincerely,
/s/ Carleton

Carleton

60a enclosure

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
November 16, 1957

Dear Sir Mac and Gray:

I write after a long silence to let you know what course our work has taken and to ask a few questions. After taking out two months for extensive patrolling which included a long patrol through the Kukukukus and crossing the island to Papua and down the Lamari, Subu and Purari to the Papuan coast--thence to a Kuru Conference in Moresby which we organized with Dr. Scragg and Dr. Gunther--I am finally back at Moke-Pintogori in one of the most rushed and hectic periods of the kuru study. I am trying to make a complete reevaluation of all 100 or so surviving kuru patients and to make extensive new therapeutic trials of drugs as well as to collect an immense load of urines and blood, CSF, and autopsy specimens for new studies--some of which I hope to get to shortly in the U.S. This, then, is a rushed month in which we are trying to recapitulate the first four months of kuru study and to extend our investigations further.

I have your letter, Sir Mac, of September 27. It has been waiting for me for well over one month. The first kuru report is out, I believe, in the New England Journal of Medicine and the paper for the Medical Journal of Australia should shortly be out. However, we have had a great deal of trouble in our work with the latter journal in the last few days. This paper was written before pathological reports were available and when our total case summary was well under 100. As we studied the disease further and collected further cases, modifications of some importance in our view of the disease occurred and also, the pathological reports became available. I informed the editor that I wanted to revise the paper somewhat to include these later findings; there was plenty of time, and I had already so revised the American paper which has appeared with at least the most important revisions. I hoped to edit galley proofs leisurely and to make the necessary changes and additions to them. Now, I find the editor is suddenly in an unpardonable rush to print. When I rushed air mail the revision on a corrected copy of the manuscript he telegraphed back to my cable that he could not wait for them and was rushing to print this month. I cabled our DEMAND to see and correct galley proofs first. They have now arrived and on them he sets a return deadline only a few days after their dispatch of November 13. We received them only on November 14 and 18 hours later on November 15 they were already back in Lae with full editorial corrections and revisions including addition of pathological findings, revision of case numbers to coincide with those reported in pathological reports, etc. However, since proofs arrived with his

plans, stated in a note to rush publication even before our corrections could be received in Sydney, which will be Monday or Tuesday, I suspect; we have cabled him our refusal to permit publication without receipt and following of our corrected galley proofs. This is the first time in my life I have been denied the right to see and correct galley proofs. We are perfectly willing to lose priority in publication and have the paper even months from now. Furthermore, we would rather withdraw it from publication than have it appear without our revisions. Since the journal is going to give it immense space and publish with it 12 or 13 illustrations, it certainly is in the interests of ourselves and of the journal to have the article up to date, medically sound and scientifically accurate. Should the editor not heed our pleas and publish without our corrections we shall be unwilling to publish another word of the kuru story in Australian journals and we shall be forced to modify, restate and retract much of what he publishes in American and European journals.

I tell you all this, Sir Mac, in the hope that you can advise him to give us the benefit of a few days delay in this panicked rush to print, and make all corrections and revision we have marked on the galley proofs. There is no hurry from our point of view. We can wait even months before the paper appears. I realize that the horrible publicity which the radio and press have given to kuru is the cause for his rush, but premature, unedited publication will only confuse the issue and reflect poorly on the journal. To our horror, manuscript material marked "confidential, restricted, not for release" (because it had been submitted for publication) has been released in Port Moresby to press and radio and I read full quotations from our papers in press. You can imagine my anger when I see paraphrasing of my very statements--often printing without paraphrasing--in Sydney newspapers when the statements were made only in confidential manuscripts submitted to journals for publication. In view of this hideous blunder by whoever dropped our manuscripts or their contents into press hands--a full breach of medical and scientific ethical procedure--we would like the Australian article to be at least as accurate and up to date as the Sydney Herald and Time. On this matter, then, Sir Mac, we would be most grateful to you for any help. We have made all corrections we seek to make both on a revised copy of the original manuscript which should already be in the editor's hands and again on the galley proofs which he will have received before you get this letter. Enough of all this.

Kuru cases seen and studied by us now exceed 200. Our deaths from kuru among these 200 number over 50 already. The problem of mild, incompletely expressed cases of kuru is now receiving considerable attention from us for we have a number of mild, uncertain cases which "recover" or remain stationary. Thus far no full-blown, advanced case has survived or appears likely to do so and the same is true for fully-depressed cases of moderate severity and duration--with only the few exceptions which we believe to have been hysterical mimicry of kuru. We have, furthermore,

now tracked down another disease syndrome distinct from kuru but extremely close to it clinically and of quite a different duration and usual course. It is, however, undeniably a "close relative of kuru" and since it occurs in a different but neighboring people, I am most attracted to the possibility that we have a "genetic variant" of kuru...much as the different patterns which many of the complex heredofamilial syndromes run from one family to another affected family, which probably accounts for the mass of eponymically designated syndromes in the books.

Cyril Curtain reports finding of what may be a new or abnormal serum protein in very significant amounts in our "control" sera and he still gets--but inconsistently--very abnormal alpha and beta globulins in many kuru cases but not in controls. Thus, he is involved in the immense problem of the globulin and serum protein patterns in Melanesian natives and to sort out all the infectious, environmental (dietary) and genetic variables which may influence the picture will be a hard task. I think he may really have a lead in kuru but I am most cautious, since until the full story of globulins in this and surrounding populaces in "normal" individuals has been worked out, the rather frequent globulin "abnormalities" in kuru cannot be interpreted.

Our work on toxicology and ethnobotany and study of all dietary and contact and bite exposure to insects, spiders, etc. is intensified--but no good leads thus far. We put a full boundary around kuru by well over 1000 miles of hard walking, interviewing for weeks on end, and mountain climbing. I have tracked down as well as I can in this brief time all memory-recorded kuru deaths in the past and have place, age, sex, and family history data on each.

We are most anxious to know of any results on the urine amino acid studies which were done on further urine collections sent down to Gray for transmission, I believe, to the Women's Hospital. Furthermore, we would like any further word on neuropathological finds and on pathology of other tissues received. I have written my thanks to Dr. Graeme Robertson for his note. To our chagrin we did not get to see a copy of his report until a Time reporter arrived carrying the full report in his notes from Moresby and showed it to Vin, to Vin's great surprise and astonishment. I was out on patrol and thankfully missed the press. However, they caught me in Moresby, unfortunately.

We are so rushed and pressed for time at the moment that I cannot write more. If the Australian article comes out with our corrections we shall be proud of it, for it has in it all we are prepared to say at the moment. Otherwise, we shall have to get the revised story off to other journals. Thank you for your interest and cooperation on the kuru problem. May we hear from you shortly?

Sincerely,
/s/ Carleton
D. Carleton Gajdusek

Okapa Patrol Post,
via Kainantu,
Eastern Highlands,
New Guinea
17th November 1957

Dear Joe,

Enclosed are extensive Fore food lists which represent part of the fine work Lucy Hamilton has been doing with us on Kuru. Lucy we stole from the Department of Health for Kuru work, hung on to her tightly when they cabled for her return, and now, after a Kuru Conference in Moresby, we have her again for two weeks. However, she is about to be married and lost to both the PHD and Kuru--to the latter temporarily only, I hope. Since our time is short, we are rushing ahead with intensified studies and a feverish attempt to document, record, and summarize all of our findings before our project breaks asunder. Lucy has only a matter of ten days more with us and she is working with me on a full write-up of her findings and correlations of them with our epidemiology, case findings and clinical studies. We have just had Kevin White, the Lae botanist, here assisting in field botanical work and collections, and he has helped in the revision and final preparation of Lucy's extensive lists, which I am submitting to you now for:

1. Permanent file with the Kuru records (one copy);
2. Dissemination through NIH to all who may be able to contribute (physiologist, pharmacologist, toxicologist, etc.) to the problem by survey of these records (1 copy);
3. Transmission (on loan) of one copy to the Smithsonian botanists and entomologists and mycologists (the third copy) for their comments on possible toxicology, alkaloid content, etc. and, later, to any toxicologists and pharmacologists who may be able to contribute ideas, and later to other museum groups.

Lucy and I are now preparing a full epidemiological evaluation of the Kuru problem as far as it has thus far been worked out. We are working it up section by section. Soon the section based on her Fore dietary survey will be written. Thereafter, the sections on food consumption and strange and exotic foods by the Kuru and non-Kuru Fore, and also a comparison of Fore with other surrounding linguistic groups as to food usage (including native salt preparations, body paints, drugs, etc.) will be prepared. We are also working out both a detailed epidemiology on the Moke community in respect to Kuru over recent decades and the present, and the large scale epidemiological pattern of Kuru over the entire Kuru region. These and other individual sections will eventually be incorporated into a series of Kuru epidemiology papers by Vin, Lucy and myself; it is in a mad rush to get the immense sheaf of data recorded in better order and, at least, temporarily analyzed that we are now rushing furiously ahead. Back in Washington, I shall work up the papers definitively and keep in touch with Vin and Lucy by mail. If we are successful, all the data for the final paper

preparation should be ready for transmittal to the Kuru record file at NIH (which awaits me there, I trust) within the next few weeks. These lists of Lucy's are part thereof.

We are sending out via Qantas a shipment of plants which are summarized on the accompanying sheets. These are for immediate study. Kevin White is just completing a week of botanical work with us and has made these collections for your study and, particularly, toxicological, pharmacological analyses. These two plants have not been linked specifically with Kuru, but of the entire Fore dietary list they appear as most suspicious at the moment.

We are proceeding on the assumption that women and children of both sexes--even older boys who no longer stay with the women in the gardens--differ from men in their exposure in that they (i.e. the women and children) may be prone and accustomed to eating some plant, insect, etc., uncooked in the gardens and bush as they go about their daily lives. Adult men may have already abandoned largely this propensity. Just what it might be, we have not been able to spot. The shipments en route are those of most toxicological and medical interest in Fore diet and their possible relationship to Kuru must be ascertained.

Although I now have further cases of women from low-Kuru incidence communities developing Kuru in the Kuru region, I have obtained these along with a host of new cases of Kuru region women developing Kuru outside the usual Kuru region, or in regions of low-Kuru incidence, but none have ever developed it really far away. One adult male patient got the illness working in a calaboose fully one day's walk outside the furthest boundary of the Kuru region, although he comes from the center of the Kuru region. In the calaboose it is most unlikely that he had any dietary exposure different from all the others. Thus, as with a number of other cases, we are forced to conclude that the lesion, if toxic, is inflicted early and without producing associated symptoms and then proceeds over the course of many months to mounting neuronal destruction without subsequent exposure to the toxin causing the original insult. Cases such as the woman who progressed from earliest Kuru to fatal termination in Lufa, miles away from any site where Kuru was previously known in a Kuru-free populace, and our current cases progressing in our Kuru hospital when taken fully out of their bush and village setting and, it appears, even the cases we have had in Kainantu fully out of the Kuru region. All these make it most necessary to consider some accumulated and then slowly released toxin (perhaps a metal or rare earth, etc.) or some material which continues over many months to act after initial exposure.

Finally, I can still see no sign of infection or post-infectious phenomenon, but with something as unique and unprecedented as Kuru a unique and unprecedented explanation is required. Thus, I continue to wonder whether some arthropod-borne vector might not be transmitting an agent causing an asymptomatic sensitizing infection (like von Economo's sleeping sickness, but clinically less apparent) and, finally, I wonder whether some neurotoxin akin to that of "tick paralysis" might not result from arthropod bites or ingestion (insects and spiders). Finally, is any arthropod ingestion likely to

- 3 -

give rise to neuroallergic response? Cannibalism as a possible source seems well ruled out.

We are sending you also shipment of clotted bloods in sterile 30 ml venules from Kuru cases, along with a few exactly similarly collected controls. These are the most critical specimens we can collect. I suggest designating them for trace metal studies, including even rare earth, if such things can be done, for we are really looking for the proverbial "needle in a haystack". If these arrive in such condition that serum specimens can be easily and well removed, wire me information and I shall then send similarly fresh Kuru blood specimens from a host of Kuru cases as the final supply of specimens for the Kuru file. An immense serum file assembled in Melbourne should be under way to you already, and further shipments will also be off. These are designed for serology and any chemistries still worth doing. However, these specimens I now suggest sending directly as clots in venules, planning as we now have on a really tight air express, refrigerated delivery schedule are designed to provide fresher serum and clots for any more critical toxicity or chemical studies. If you wire me about whether the first trial shipment warrants a second, also wire about condition of fixation and receipt of the last shipment of two trace metal-free brains. Another trace metal-free formol saline fixed brain is here hardening and awaiting shipment.

A short cable address:

GAJDUSEK
OKAPA
KAINANTU
NEW GUINEA

What is a short cable address for you?

Sincerely,

/s/Carleton

D. Carleton Gajdusek

(NIH)

November 21, 1957

AIR MAIL

Dear Carleton:

It is good to learn that you plan to return to the States in December. I hope nothing comes up which will interfere with those plans since the National Institutes of Neurological Diseases and Blindness staff is taking steps to appoint you as a Visiting Scientist for a one-year period beginning just after Christmas. The salary level will be equivalent to that for a GS-14 Medical Officer, i.e., \$10,320 per year. I hope these arrangements are satisfactory to you. We are looking forward to having you here and to the papers which you will put together from all of the data collected in New Guinea.

I am enclosing information on identification of some of the plants we received from you. We have received two shipments of plants, and chemical work on them is continuing. Currently Dr. Horning is checking on the occurrence of glycosides in these materials. Dr. Masland in NINDB has been having some difficulty finding anyone who is set up to perform the trace-metal studies for those elements mentioned in your letters. Copper is the only one being determined at NIH. However, he believes the laboratory at Fort Meade will probably be able to do the determinations.

Mrs. Beyersdorfer in NINDB has already informed you of the receipt of film and the production of prints. By now you should have received the 12 prints made from the latest batch of negatives which we selected for you. It has been our assumption that these 12 are for your use in writing a new paper on kuru. By now the Medical Journal of Australia must have received the prints sent from here. If this is not the case, perhaps you can use some of the 12 illustrations sent you by Mrs. Beyersdorfer in which case we could then send you different prints.

Also enclosed is a copy of your paper in the New England Journal of Medicine. The reprints are not yet available, and you will probably be here before they are.

Although I appreciate conditions are difficult where you are, I am afraid you have been remiss in providing proper information to those groups performing anatomical studies for you. Some of the people in Australia were disturbed to learn that studies similar to those they were making were being performed by others simultaneously without their

knowledge. They were particularly concerned because they have only limited technical help available. Furthermore, they were concerned that they had no acknowledgement from you of their reports on the anatomical studies. Please see that both groups are informed more thoroughly of what the other group is doing.

Please keep us informed of your time of arrival in order that planning may proceed satisfactorily. NINDB will make space available for you for the writing of a series of papers on kuru. All the material sent by you is on file awaiting your return.

With kind personal regards.

Sincerely,

/s/ Joe

Joseph E. Smadel, M.D.
Associate Director

Dr. D. Carleton Gajdusek
c/o Department of Public Health
Port Moresby, Papua
Territory of Papua and New Guinea
(at Okapa Patrol Post, via Kainantu, New Guinea)

Enclosures (2)

OENANTHE JAVANICA

Parcel No. 1 contains the fine leafed form.

" " 2 " " normal broad-leafed form.

The fine-leafed form is mixed with the latter in gardens and in the rain forest, but is not common. The natives make no distinction between these forms and graduations exist between the extreme types.

Webb, in his guide to the Medicinal and Poisonous Plants of Queensland, lists O. orocata and O. phellandrium. The former has oenanthe-toxin, which is toxic, resembles cicutoxin in action, acts on the spinal cord. It causes stomatitis and paralysis. The latter causes paralysis also.

References

- Merck 1940. The Merck Index (Merck & Co., Inc., Rahway, N.J.) page 390.
- Pammel, L.H. A Manual of Poisonous Plants Chiefly of N. Eastern North America. Torch Press, Iowa, pp. 649-650.
- Potter, H. 1932 Potter's Cyclopaedia of Botanical Drugs and Preparations - 4th Edition. Potter and Clarke, London, pp. 357-358.

No. 2 parcel contains material identical to that of No. 47 of the Dietary Food List collected by Miss Lucy Hamilton.

GABULIMIMA BELGRAVEANA

Parcel No. 3 contains fruits of this species. Bark and leaves have already been forwarded and this present collection corresponds to No. 177 of Miss Hamilton's Dietary Food List.

The leaves and bark or fruits are eaten to induce the "dream man" state, in which the location of enemies or game is supposed to be revealed.

62a enclosure

OFFICE MEMORANDUM

November 12, 1957

To: J.E. Smadel
Associate Director (Intramural Affairs), NIH

From: P. Bailey
Director, NINDB

Subject: Dr. Gajdusek's project

Dr. J.G. Greenfield, Visiting Scientist, has expressed concern about lines of communication between Dr. Gajdusek and the Australian group in New Guinea. Attached is a copy of correspondence from Dr. E. Graeme Robertson, neurologist and neuropathologist from Melbourne, to Dr. Greenfield (October 31, 1957), and to Dr. R.F.R. Scragg, Acting Director of Health, Port Moresby (August 16, 1957).

Dr. Robertson received the first sections of brains from Dr. Gajdusek, attached is a copy of the report which he forwarded to Dr. Scragg with a copy to Dr. Gajdusek. According to Dr. Robertson, no acknowledgment was made by Dr. Gajdusek and he was not advised of the brains being sent here until he heard from Dr. Greenfield.

Dr. Greenfield states that we have sufficient brains (12), which have been studied to date, to establish the disease from a pathological standpoint. What remains to be done is essentially epidemiological, and more precise clinical studies.

Do you have any suggestions to better relations between Dr. Gajdusek and the Australians?

/s/ Pearce Bailey

Pearce Bailey, M.D.

Attachments

33 Collins Street
Melbourne, C.L.

31st October, 1957

Dr. J.G. Greenfield,
National Institutes of Neurological Diseases
and Blindness,
Department of Health, Education, and Welfare
Bethesda 14, Maryland

Dear Dr. Greenfield,

Many thanks for your letter. I can only make one response - that science must go on! I am sure that you will do it infinitely better, and with far more authority, than I could. I was asked to examine the specimens by the Walter and Eliza Hall Institute, and it was hoped that I should go to New Guinea to study the patients neurologically. My only interest was in trying to solve problems. I suppose that I would have been able to do it as well as the Murray Valley Encephalitis paper.

The sections I showed you were from a brain which had already been cut up in New Guinea, and we now have many sections from two intact specimens which were sent later.

I sent reports on the first specimen to the Director of Health (Acting) in New Guinea, with a copy for Gajdusek, which was not sent on, and then a copy direct to Gajdusek when a telegram from him asking for the findings arrived - but I have had no reply from either. It does seem reprehensible to send specimens to two places without informing the other, if only because of the work involved, for we haven't unlimited technical help and I have to sweat over the sections, owing to lack of continuous experience.

The only intimation to the Walter and Eliza Hall Institute that Gajdusek had sent specimens elsewhere was quite recent. I am baffled by it all, and obviously do not understand all the facets - therefore the less said the better. I have mentioned my reaction to Sir Macfarlane Burnett and he agrees about it.

Thank you so much for sending me the informative proof - it was something which many others would have forgotten to do.

It was so nice seeing you and Mrs. Greenfield again. With kindest regards,

Yours sincerely,

/s/ Graeme Robertson

62c enclosure

16 August 1957

Dr. R. F. R. Scragg
Acting Director of Health
PORT MORESBY. Papua.

Dear Dr. Scragg,

I enclose a preliminary report on the pathological appearance in Brain I. It had already been cut into slices, which contributed to the difficulty of examination. The second specimen, apparently preserved as suggested, was in excellent condition. Its examination has been commenced. Again, it was macroscopically normal. Embedding in celloidin takes some time, but a report will be sent with as little delay as possible.

While abroad I took the liberty of showing some sections to Dr. J. G. Greenfield and Dr. Webb Haymaker. The notes comprise all opinions.

Yours sincerely,

/s/ Graeme Robertson

E. Graeme Robertson

THE ROYAL MELBOURNE HOSPITAL

Department of Neurology and Neurosurgery

16th August, 1957

PRELIMINARY (INCOMPLETE) REPORT ON CASE I.

Macroscopically brain appeared normal.

Frozen, paraffin and celloidin sections.

Cerebellum shows most pathological change.

Patchy degeneration of Purkinje cells (probably number lessened:
In order cells essential cellular structure has disappeared:
silhouettes of nuclei, some cells shrunken and pyknotic).
Changes appeared more marked in neo-cerebellum.

Bergmann layer cells look alright.

Molecular layer - increase in glial nuclei: swollen fat-laden microglial cells (gitterzellen) in small numbers, patchily distributed. Appear to be most numerous when Purkinje cells most affected. In one place marked thinning of the molecular layer with degenerative changes and gitterzellen. Some gitterzellen seen under pia, but no marked meningeal accumulation.

Granular layer - reduction in nuclei - some cells pyknotic. More gitterzellen than in molecular layer, in greatest concentration where grey matter abuts on white. Increase in astrocytic nuclei.

Dentate nuclei - neurones normal. No gitterzellen.

Roof nuclei - some cells vacuolated and shrunken.

White matter - ? some axons swollen. Few macroglial cells around vessels.

Cerebral cortex - slight abnormality. Some degenerative changes in neurones which might even be like post-mortem changes. ? More horizontal cells in layer V than normal. Axons appear swollen in places.

Basal ganglia - very little change. Few gitterzellen in neighbouring white matter, of perivascular distribution, but concentrations rare.

Medulla - some mucinoid bodies in white matter of medulla. Dr. J. G. Greenfield pointed out the similarity of these to those found in grass sickness in horses. May be artefact. Otherwise no definite change.

Glia and myelin stains still to come.

Summary: Changes surprisingly slight - most marked in 'cerebellum - regressive changes with degeneration and disappearance of Purkinje and granule cells, with microglial scavenger activity and astrocytic proliferation. Changes would appear to be of no great age. The process is not acute and does not appear to be inflammatory.

/s/ E. Graeme Robertson

OKAPA PATROL POST
 via Kainantu, Eastern Highlands
 Territory of Papua and New Guinea
 November 24, 1957

Dr. J.E. Smadel, Associate Director
 National Institutes of Health
 Bethesda, Maryland
 U.S.A.

Dear Joe,

Enclosed is a list of Kuru blood specimens off to you for trace element studies in sterile venules. Controls can easily be collected similarly and sent along with other Kuru bloods. These were delayed inadvertently, and missed one plane connection, and thus we can hope for even prompter transmission on most future shipments.

Enclosed are summary lists of recently dispatched still negatives and negatives. All undeveloped.

Enclosed are some summary sheets for Kuru and non-Kuru blood specimens sent to Melbourne for work by Roy Simmons (blood group genetics) and Cyril Curtain (abnormal hemoglobins and serum protein study by Tiselius electrophoresis and ultracentrifuge, etc.). Curtain thinks he has found a new globulin in normal Fore and real abnormalities of alpha and beta globulins in most--but not all--Kurus. I am sceptical for reasons summarized in my last long letter to him, but it is the first real lead of any sort and it must be pursued.

We are collecting mumu stones (some being beryl -containing ores and some arsenical iron pyrites, we are told) for very thorough study. When these go off to you--stones cannot be made a light shipment--they will go off with a section of our epidemiological papers in which mumu cooking is described and the use of these stones in steam cooking. Although such mumu is rather universal in the Highlands, it is possible that local stones might vary greatly and that some stones could serve to contaminate the food. Why the peculiar age distribution of cases? Well, perhaps food directly adjacent to stones in the mumu are particularly involved or a certain type of food of all those heaped into the steaming pit, and these are particularly the fondness of women and children and some men---a wild possibility, but one which needs investigating. In any event, rare earth, beryllium or arsenic in mumu stones, etc. etc., cannot solve the matter. The substance must be found in the body and thus the trace metal samples of autopsy viscera and the trace metal free brains are most critical items. Please get all we can from them. It looks as though further autopsy materials may be unobtainable. Thus, the natives have given up our medicine... they know damn well they do not work...and I am fighting (verbal battles in Fore), bribing, cajoling, begging, pleading, and bargaining for every

opportunity to see a patient, and strenuously working tongue muscles for hours for every further day we get a patient to stay in the hospital, accept therapeutic trials, etc. etc. Vin is sick and tired of the "duress of personality" which is required to pressure every case into our care and I do not like the effort. It means, however, that unless we start curing cases quickly, we cannot expect any clinical material much less any autopsy specimens. I am willing to keep up the push using every ruse short of actual duress by force and authority...that we cannot contemplate...but Vin is tiring even of the battle of personalities--between us and our Fores which our attempt to do something for the KURU victims is demanding.

We have now accumulated many further cases which make the toxic possibilities ever more limited and ever more baffling: Thus,

1. Many cases develop outside the Kuru region in Fore or Kuru-region people who have moved into the Kuru-free populace to live or work.
2. The illness progresses relentlessly even if patients are totally removed in earliest stages from the Kuru region and are on diet of the non-kuru regions.

This obviously demands that any toxic agent causing kuru must be something the Fore bring with them or find in the non-kuru regions, yet which the local residents with whom they are living are not exposed to...OR it means that a most unusual toxin exposure is involved, one in which exposure months or even years previously is sufficient to initiate a progressive slow neurological destruction.

Please see that a copy of the NEJM article gets air mailed to us--we will not see it otherwise. Excuse this barrage of correspondence. I hope you can find someone to read it.

Sincerely,

/s/ Carleton

Carleton Gajdusek

ADDITIONAL NOTES ON KURU:

November 24, 1957

Watching the illness carefully again in the past two weeks and reviewing our epidemiological and clinical findings, the two items listed on the accompanying letter become ever more convincing. Namely:

1. Cases develop outside the usual Kuru area in visiting or immigrating Fore (from the Kuru area) from weeks to years after they have left the Kuru region to reside with people who do not get Kuru. We now have several such cases.
2. The relentless progression of the illness even when removed from the Kuru region and off the usual Kuru region diet, even when this occurs in very early stages of illness. Evidence that this is so is beginning to accumulate.

Even those newly discovered communities outside the boundaries we thought we had set wherein kuru has occurred in the past, we find, are impressive in that they are communities with extensive Fore contact (presumably also intermarriage), such as Fore moving in among them or their having moved into the Fore regions during the time of intertribal warfare.

The two items noted above, taken with this added evidence for possible genetic--or at least a distinct "cultural" predilection, makes the toxic possibility look even more difficult to establish. However, if the neuronal destruction is not genetically predetermined completely, and if exogenous toxin is unlikely, is there any chance that we may be involved in a peculiar sort of autoallergic state or rheumatic-like self-perpetuating process or drug-reaction, exfoliative dermatitis-like reaction akin to Stevens Johnson disease? What I specifically wish to ask, is whether any of these hypersensitivity states might conceivably release a kindred cytological lesion--if not neurocytological?

A number of wild possibilities come to mind--some can be dismissed already. Others cannot be dismissed by any means. Thus,

1. Cannibalism with human extoderm or brain consumption might provide a year-long or life-long sensitization triggered off by consumption of raw or poorly cooked extoderm or neuronal tissue.

The Rub: Cannibalism has ceased, did not involve brain as far as we can find, and even if rare cases still occur, many of our youngest patients have rather certainly not consumed human tissue.

2. Consumption of animal brain--particularly if poorly cooked or uncooked--or, perhaps other neuronal tissue (ganglia, etc.) and/or ectodermal organs. Conceivably prolonged such exposure to raw or poorly cooked pig--especially ectoderm, ganglia or brain--might lead to a hypersensitivity state which slowly progressed or was triggered by moderate new exposure.

The Change: Fore pig--the major meat eaten--is, as is other game meat, cooked in mumu by steam cooking over hot stones or steamed in bamboo tubes. In both cases it comes out notoriously undercooked. Whether the brain is eaten or not we must still further investigate. It appears that the head is usually not opened in cooking, the brain therefore cannot be very well cooked. It is usually eaten later in household of the owner of the pig and not by those feasting, who first consume the rest of the pig. Certain men and youths definitely deny that they eat or like the brain, and I have a hunch women and children get it mostly--occasionally men--and that it may or may not be further cooked again, a day later, in bamboo tube steam cooking. Thus, repeated, long-term exposure to undercooked pig brain--perhaps particularly by the Kuru-affected age-sex group is a distinct possibility. What are the chances of this?

3. Consumption of raw meat in childhood. As a mumu is being prepared we often see small children given pieces of raw meat which they eat without cooking and without being stopped. Excessive raw meat consumption in early childhood--perhaps particularly ectodermal (since skin is always eaten) might be questioned.

Pig eating and mumu cooking are near-universal throughout the Highlands and Kuru is not. However, we do not know of eating and cooking habits referable to the brain and ectodermal organs and degree of consumption of uncooked meat. It might be a matter requiring prolonged, repeated exposure...as in brain-reactions to brain vaccines...and the matter of individual reactivity might well enter in as a genetic component--as is the case with most immune reactions.

These are wild conjectures, I admit. But take them for what they are worth and see if anyone can give us a ray of hope.

Finally, critical things like search for manganese (a most immediately essential matter) in brain and other tissues have not yet been done.

Can you let us know whether cytochemistry, trace metal studies, etc., are being arranged for and will be done on the few precious brains we have sent to you and rush any information--positive or negative--about any unusual element which might be encountered or any pertinent negatives (arsenic, beryllium, mercury, manganese, copper being already things we must know about)?

In the next air freight a few further trace metal free blood specimens and cerebrospinal fluid specimens will be off to you. These include:

CSF specimens in trace metal free specifically prepared
Aluminum-capped, rubber-washed bottles:

23 November 1957

SERI	Male, 23	moderately advanced Kuru
AOKABARA	Male, 32	Kuru-like illness, advanced, from Kawaina
AUWATNEFA	Female, 30	Kuru-advanced, near-terminal

24 November 1957

NEKISA	Female, 35	moderately severe Kuru
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25 November 1957

MARO	Female, 23	post-meningoencephalitis (control on Kuru CSFs)
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BLOOD SPECIMENS: (in 30 ml British-type vacuumatic venules)

24 November 1957

KUMPA	Male, 14	early but typical Kuru
NEKISA	Male, 24	moderately severe Kuru

25 November 1957

MARO	Female,	post-meningoencephalitis (control on Kuru bloods)
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P.S. (26 November 1957):

Our much sought after case has appeared!!! A man, who perfectly well walked to Goroka from the Kuru region (Keiagana) for work and ended up 5 months ago on the coast as a laborer who developed there on the coast Kuru now of c. 3 months duration, very typical, severe and rapidly progressive. He certainly would not have started out for work with even the slightest suspicion he had Kuru and patients themselves invariably diagnose the illness before we do. Thus it is a case with onset as far away and completely outside of the Kuru region and full, very rapid progression in three months completely removed from regions wherein Kuru has ever previously been observed. What, then, Joe, does this make of all our toxic search? You can see why I have been forced to lean genetically--for predisposition, at least.

/s/ Carleton

Carleton Gajdusek

KUMPA

Male, 14

ANUMPA

FIRST COURSE OF BAL (Oily injection of Dimercaprol) Therapy:

Given deep i-m: 0.05 gm Dimercaprol per cc of Arachis Oil containing 10% v/v Benzyl Benzoate.

24 November

13:00	URINE I	210 ml	5 bottles
15:00	BAL 1	(6.0 ml - 300 mgm)	
16:00	URINE II	300 ml	5 bottles
18:00	URINE III	150 ml	4 bottles
19:00	BAL 2	(6.0 ml - 300 mgm)	

25 November

06:00	URINE IV	300 ml	4 bottles
07:30	BAL 3	(6.0 ml - 300 mgm)	
10:00	URINE V	110 ml	4 bottles
16:00	URINE VI	225 ml	4 bottles
16:10	BAL 4	(6.0 ml - 300 mgm)	

26 November

08:00	BAL 5	(6.0 ml - 300 mgm)	
16:00	BAL 6	(6.0 ml - 300 mgm)	

27 November

08:00	BAL 7	(6.0 ml - 300 mgm)	
16:00	BAL 8	(6.0 ml - 300 mgm)	

28 November

08:00	BAL 9	(6.0 ml - 300 mgm)	
16:00	BAL 10	(6.0 ml - 300 mgm)	

29 November

This fresh, severe, rapidly advancing, previously untreated case of classical KURU has provided the best urine specimens we can get here in our kuru center. Obviously such matters as possible sudden release of stored mercury, manganese, copper, etc., could be settled by these BAL treatment specimens. Can you get as many metals sought for as possible? Can you get any leads spectrophotometrically?

CINE FILMS: 16mm--taken on Paillard Bolex provided by NIH for Kuru research

NOTE: These films were provided by NIH, bought in USA, and thus processing has not been paid for, in all cases but the two rolls of 50 feet of Kodachrome each. These 50-foot rolls were Australian-purchased and processing has already been paid for in purchase price.

These belong to the kuru file of 16mm films. I hope to edit them, if they are satisfactory, into a full film on my return. Thus, please do not let the originals be shown--but prepare a copy for editing and for showing to interested collaborators at NIH.

FILM NO 19: Cine Kodachrome - daylight type - 50 feet. Purchased in
Lae, New Guinea

Exposed: 16 November 1957 at Moke-Pintogori; 24 frames per second.
Bright sun with or behind or to side of camera and openings
between 4.5 and 6.3 used for all shots. Wider open for close
ups of dark-skinned subjects, stopped down to 6.3 for distant
shots, average subjects.

Subject matter: Two shots of Kuru research center Hospital from
Kuru research office residence. The new office
treatment building is under construction in front
of large new Kuru Ward. View of Kuru patients
in front of Kuru ward.

Patients sitting from left to right, along wall
of hospital:

NAGOIA	F, 40	moderate
ASISI	M, 11-12	rapidly deteriorating
AOGA	F, 9	prolonged course
NATA	F, 8	prolonged course
INARE	F, adult	near terminal
TETE	F, adult	moderate
NOGA	F, adult	mild, slowly progressive
AMARERE	F, 40	severe
PESORITME (PESO)	F, adult	near terminal

In all pictures these 9 patients are studied.
We have failed to record each shot, but it should
be easy to identify patients. Nagoia was very
little photographed, the three children were
extensively photographed. Inare was extensively
photographed.

This first film shot without turning back film guides
inside camera. This may effect film???

FILM NO 20: Cine Kodachrome - daylight type - 50 feet. Purchased in
Lae, New Guinea.

Exposed: 16 November 1957 at Moke-Pintogori; 24 frames per second.
Same as Cine Film No 19 in exposure, etc.

Subject Matter: Same as above. Same group of 9 Kuru patients studied.
ASISI, Male, 11 to 12 years old held up by Vin Zigas.
Much of film concentrates on him and upon AOGA and
NATA, the two girls. They have continued to remain
obese and breast development, initiated with
cortisone and delta hydrocortisone therapy, has
continued even after medication has long since ceased.

FILM NO 21: Cine Kodachrome - daylight type - 100 feet.

Exposed: 16 November 1957 at Moke-Pintogori.

Subject Matter: Same group as in above two films, filmed at same time.

Film largely close-up studies of these subjects.
Facies especially.

NOTE: Films are undeveloped and require processing. Do not open and
inspect before processing!!!!

Two 35mm still films undeveloped for developing and printing into Post card
size for Kuru film file.

Please number negatives appropriately--but I have, for the moment, lost track
of the number of the last negatives sent for the still film Kuru film file.

The film is good 35mm Plus-X film rerolled into Panatomic X cassettes. In
developing this can be borne in mind. It is undeveloped.

Two films exposed on 16 November 1957.

Multiple views of Kuru patients then in hospital at Moke. Same series of
patients reviewed in Cine Film Nos. 19-21 inclusive.

Joe: Please consider some of these shots for publication, if you have had
difficulty selecting proper photographs for the German article.

63a appendix

To: Joseph E. Smadel, M.D.
Associate Director, NIH (Intramural Affairs)

December 24, 1957

From: Richard L. Masland, M.D.
Assistant Director, NINDB

Subject: Comments on Dr. Gajdusek's letter dated November 24.

I have reviewed with great interest Dr. Gajdusek's most recent letter of November 24 regarding Kuru. The data which he provides seems very effective in ruling out a genetic disorder, since this disease does not appear in closely intermarried communities outside of the Fore region. He also rules out a toxic factor in indicating that people emigrating from the Fore area develop the disease after they have left, and that the disease progresses in spite of the removal of the patient from the affected area. I wonder if we have adequately ruled out the possibility of infection. Dr. Gajdusek mentions that the meat which these people eat is usually grossly undercooked. I am thinking of a parasitic disease such as toxoplasmosis, but involving some other as yet unrecognized agent. I know that efforts have been made to culture organisms from this material, but I wonder if adequate consideration has been given to a parasitic disorder. I must confess that the pathological findings which indicate a diffuse degenerative process without inflammation are much against this, but it could be that we are dealing with an unusual reaction to some parasitic invader. This is a wild chance, but evidently this disease is a wild one.

/s/ Richard L. Masland

Richard L. Masland, M.D.

Dictated but not read

OKAPA
28 November [1957]

Dear Joe,

Just a set of papers to be filed away with the Kuru files until I get there to begin to make sense out of them. Vin and I are pleased to see that most--not all--of our corrections came out in the Australian Journal at the expense of a few of the cuts. It looks OK and we shall make all the later additions and corrections in the German article. Thank you for the black and white photos for the German article. These enclosures may be of interest. One is a case history which should be fully stapled together. Others are trace metal reports of which I retain copies here. I would not dismiss metal possibilities on the basis of them alone. Finally, there are a few reports which we shall need on hand in preparing the final record analyses of the work Vin and I have been doing.

Sincerely,

Carleton

64a enclosure

P.J. Southern, Esq.
Soils Chemist
Department of Agriculture,
Stock and Fisheries
Port Moresby, N.G.

17 July, 1957

Dear Mr. Southern,

The spectrographic survey of the ashed blood and tissue samples from sufferers from Kuru disease has now been completed and the report is attached hereto. I am also forwarding a copy of the report on the samples submitted by Dr. Anderson of the Walter and Eliza Hall Institute. I presume you have the key for identifying the samples.

The analysis is, of course, qualitative at this stage although any heavy metal present in significant quantity should have been detected. The compositions appear to be fairly normal to us, but if you wish a quantitative estimation of any specific element in any particular samples, I would be glad if you would let me know at your earliest convenience since the equipment will be reorganized for some rather different investigations of our own.

I trust that this information is of some assistance to you although it is evidently negative insofar as metal toxicity is concerned.

Yours sincerely,

A.L.G. Rees
Assistant Chief of Division
of Industrial Chemistry
Commonwealth Scientific and Industrial
Chemistry, Melbourne

Chemical Physics Section, Division of Industrial Chemistry

C. S. I. R. O.

Spectrographic Analysis of Solutions
derived from ashed blood and tissue
samples from Kuru disease sufferers.

Spectrographic analysis of the solutions has revealed the presence of the following elements:

No. 1	Fe Mg Ca K Al Na
2	Fe Mg Ca K Al Na
3	Mg Ca K Na
4	Mg Ca K Na
5	Mg Ca K Na
6	Mg Ca K Na
7	Fe Mg Ca K Al Na Cu
8	Fe Mg Ca K Al Na Cu Mn
9	Fe Mg Ca K Al Na Cu Mn
10	Mg Ca Na
11	Mg Ca K Na
12	Mg Ca K Mn Na
4A	Fe Mg Ca K Na Al Cu
7A	Fe Mg Ca K Na Al Cu Mn
12A	Fe Mg Ca K Na Cu Mn
26	Fe Mg Ca K Na Cu Al
29	Mg Ca K Na Al
39	Fe Mg Ca K Na Al
46	Fe Mg Ca K Na Al
53	Fe Mg Ca K Na Al Cu Mn
65	Fe Mg Ca K Na Cu
76	Fe Mg Ca K Na Al Cu
83	Fe Mg Ca K Na Al Cu
99	Fe Mg Ca K Na Cu

A. Walsh

B. Russell

17th July, 1957

Chemical Physics Section, Division of Industrial Chemistry

C. S. I. R. O.

Spectrographic Analysis of ashed blood
and tissue samples from Kuru disease
sufferers.

Spectrographic analysis of the samples indicated the absence of any unusual or toxic metals. In the blood samples, where a comparison was possible, no differences in metal composition were found between Kuru patients and control patients. Since no controls were available for the pathological specimens, no anomalous concentrations could have been detected, but qualitatively their compositions do not appear to be irregular. A detailed list of the specific elements detected is given hereunder:

Blood Samples

Anuna	Fe Mg Ca Na K Al Cu
Erikrepme	Fe Mg Ca Na K Al Cu
Masona	Fe Mg Ca Na K Al Cu
Numbolete	Fe Mg Ca Na K Al Cu
Asomeia	Fe Mg Ca Na K Al Cu
Aveto	Fe Mg Ca Na K Al Cu
Ewanta	Fe Mg Ca Na K Al Cu
Ia'i	Fe Mg Ca Na K Al Cu
Iamogi	Fe Mg Ca Na K Al Cu
Taranto	Fe Mg Ca Na K Al Cu
Yoboiuta	Fe Mg Ca Na K Al Cu

Pathological Specimens (Yo'eia)

Psoas Muscle	Fe Mg Ca Na K Al Cu
Kidney	Fe Mg Ca Na K Al Cu Mn Zn
Bile	Fe Mg Ca Na K Al Cu
Spleen	Fe Mg Ca Na K Al Cu Mn
Liver	Fe Mg Ca Na K Al Cu Mn Zn

A. Walsh

B. Russell

17th July, 1957

64b enclosure

The Walter and Eliza Hall Institute
of Medical Research

19th July, 1957

Mr. P.J. Southern
Soils Chemist
Department of Agriculture, Stock & Fisheries
PORT MORESBY

Dear Mr. Southern:

I have just received the 2 reports from Dr. Rees, which I am sure you also have received.

The samples we submitted were numbered and I enclose the key.

As you will see of the 9 kuru bloods all contained copper at the level detected by Dr. Rees and 3 contained managnese. Of the 3 control bloods from Okapa none contained either copper or manganese according to their test. I have spoken with Dr. Rees on the phone and he will proceed to quantitative estimation of copper, and possibly manganese on these bloods.

With best wishes.

Yours sincerely,

(S. G. Anderson)

Copy to Dr. A.V.G. Price

Copy of Ashing to June 15, 1957

Bottle No.:

1	"Liver"	5.7g		grans		
2	ARANAKA	III	urine	10g		Kuru
3	NATA	I	--	10.1g		Kuru
4	ATONA	I	--	10.3		Kuru
5	ARANAKA	I	--	10.2		Kuru
6	ARANAKA	II	--	10.0		Kuru
7	TASI KO	III		10.0		Kuru
8	YANI	II		10.0		Kuru
9	TASI KO	II		10.2		Kuru
10	ATONA	II		10.1		Kuru
11	NATA	II		10.0		Kuru
12	ATONA	III	urine	10.0		Kuru
4A	AVETO		blood	11.5	25.5.57	Kuru
7A	YOB AIOTU		"	16.0	undated	Kuru
12A	ASO		"	10.3	20.5.57	Kuru
26	EREIO		"	9.5	20.5.57	Kuru
29	MASASA		"	11.8	20.5.57	Control
39	TAKA		"	10.4	20.5.57	Control
46	IVUTI		"	13.0	20.5.57	Control
53	AWANI		"	12.4	20.5.57	Kuru
65	INARE		"	10.2	20.5.57	Kuru
76	YOEIA		"	9.5	20.5.57	Kuru
83	IAMOGI		"	10.1	25.5.57	Kuru
99	TARANTO		"	12.3	25.5.57	Kuru

P.J. Southern, Esq.
Soils Chemist
Department of Agriculture,
Stock and Fisheries
Port Moresby, P.G.

31 October, 1957

Dear Mr. Southern,

I am forwarding herewith the report on the estimations for copper in the ashed blood samples. The differences between controls and samples from kuru sufferers that were suggested by the exploratory spectrographic analyses do not appear to be substantiated by the quantitative atomic absorption results. I suspect that this arises from the fact that the concentrations of copper are very close to the limits of detection.

I am forwarding a copy of this report to Dr. Anderson.

Yours sincerely,

A.L.G. Rees
Assistant Chief of Division
of Industrial Chemistry
Commonwealth Scientific and Industrial
Chemistry, Melbourne

Chemical Physics Section, Division of Industrial Chemistry

C. S. I. R. O.

Copper Estimations of Blood Samples

(a) Solutions provided by Walter and Eliza Hall Institute

<u>Soln. No.</u>	<u>% Cu x 10⁴</u>	<u>Soln. No.</u>	<u>% Copper x 10⁴</u>
4A	2 + 0.5	46	1.5
7A	2	53	1.5
12A	1.5	65	2.5
26	1.5	76	1.5
29	2	83	1.5
39	1.5	99	4

Since there is no record of the final volumes of the ashed solutions, the concentrations of Cu in the original biological fluids cannot be calculated.

(b) Dry Ashed Samples

<u>Name</u>	<u>Concentration in Dry Ashed Blood</u>	<u>Concentration in Original Blood</u>
	<u>% Cu x 10^{3*}</u>	<u>ug/100 ml</u>
Anuna	5.5	60
Asomeia	7.5	65
Aveto	7.0	55
Erikrepme	6.0	60
Ewanta	9.5	85
Ia'i	5.5	55
Iamogi	8.0	75
Masona	6.0	55
Numbolete	6.0	70
Taranto	9.5	85
Yoboitua	7.5	75

Maximum Error 30%

* Figures corrected for reagent bland of $1 \times 10^{-3}\%$ Cu.

A. Walsh

B. Russell

64d enclosure

Paoli, Pennsylvania
20 November 1957

Joseph Garland, M.D., Editor
The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

Dear Doctor Garland,

I read with interest in the November 14 issue the Special Article:
Degenerative Disease of the Central Nervous System in New Guinea, etc.

I would like to ask the authors if there is any chemical evidences
in the blood of a chronic magnesium deficiency? In their cooking or
fires would there be any chance for chronic inhalation of zinc fumes
or zinc ingestion? Is there any chance for chronic mercury salt inges-
tion, like cinnebar-HgS? Have blood zinc and mercury levels been done
on all the ill studied? Chronic zinc and mercury poisoning will give
Parkinson-like changes and magnesium deficiency will also give rise to
obscure similarities.

Sincerely yours,

/s/ Perk Lee Davis

Perk Lee Davis, M.D., F.A.C.P.

PLD/ms

OKAPA PATROL POST
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
[December 1957]

Dr. J.E. Smadel, Associate Director
National Institutes of Health
Bethesda, Maryland
USA

Dear Joe,

With the first jeep to go out in ages about to depart and leave me alone once again among the Fore and Kuru, I am rushing off this note. Rains are blocking our tracks, and soon transport may be a dreadful problem. I lost a jeep over a cliff in a landslide in my last attempt to save time on the Purosa "road" to the south and cut by driving a few days off the walking, and the rescuing of it cost me more trouble than the walking would have. However, we are now collecting the last of those specimens I shall get here and in a few days the first two of the 4-man Adelaide team will arrive. I shall stay on to get them oriented in the problem and leave. They have 2 months for the work only and I have no clue as to how well and elaborately equipped they will be. I hope, however, that they will have extensive laboratory facilities for stepping up some of our bedside clinical investigations.

Enclosed is a list of specimens going out with this letter and to be shipped from Kainantu as soon as the flooded strip permits a plane to land by drying off a bit. The urines were really hell to collect, and full protocols on volumes and time of collection, and BAL dosage will be sent in my next letter and will also appear on the patient's charts. Thus, ALL the necessary data will be in your hands.

I have saved 3 bottles (c.90ml) of urine from each voiding--all collected in trace-metal free water rinsed kidney dishes with as little debris and wind-borne "crud" in them as is possible under these bush conditions--even our roofs have a constant "fall-out". They certainly are the last such set there will be for awhile, and I suggest settling manganese and other metal possibilities with them (mercury, etc., etc.) if possible. Furthermore, if there is adequate volume of any specimens for any amino acid or other studies, use them also for that, for they are refrigerated from very shortly after collection.

Bloods are sent on clots. Trace metal studies, obviously, are still of principal interest. However, anything which anyone can think of which may help would be welcomed. Perhaps some may have sera adequate for further Tiselius and UC studies to confirm the extremely high beta, alpha and gamma globulin patterns which Cyril Curtain continues to report from Melbourne.

All bloods are collected with only ether cleansing of forearm. This may not always get through all the dirt and pig grease between us and the patient's vein which the needle must penetrate.

The summary items which make the toxic possibilities more than ever intriguing and difficult to track down were listed in my last letter to you.

Brains on two patients are still hardening and tissues are sent herewith for immediate study. The brains which have been trace metal-free collected have been fixed with very limited volumes of formal-saline. We have very little of the precious stuff on hand. One is now sitting in a similar small volume of 5% formol saline and I shall let it fix for a long while. The other is in regular (not trace metal free) formol saline at 10%, at that, and will be hard as hell. IF anyone at NINDB believes there is value in further pursuing the quest for trace metal free brains, they had best rush appropriate containers and formol saline to us for no stills (glass stills for such critical work) can be found in the Territory and what we have we have had to get from Melbourne.

Thanks for all the steady flow of information. Anything else in pathology as yet?? Enclosed is also a Fore diet summary which Lucy and I worked up before she left us. She did all the weighing and food study, but from the limited data, nothing further could be calculated. This is to be part of a series of 3 papers on Kuru epidemiology we are writing and thus please keep it in the file.

Sincerely,

/s/ Carleton

BLOOD SPECIMENS FROM KURU PATIENTS:

Bleedings of December 4th and 5th----on Patrol to bush-hamlets

In 30 ml British-type Vacuumatic venules

Tagama	- near terminal
Tovepi	- advanced
Gitara	- advanced
Atogori	- advanced

In 8 ml British-type Vacuumatic venules

Karawani	- Kuru
Peria	- "
Kogota	- "
Kogome	- "
Pitotigi	- "
Aguane	- "
Nonota	- "

Bleedings of December 7, 1957

In 30 ml British-type Vacuumatic venules

Ake	Moderate Kuru (after 1 day intensive BAL Rx)
Seribe	severe Kuru
Tuka	severe Kuru
Amakiora	mild, slowly progressive Kuru

URINE SPECIMENS FROM BAL THERAPY OF 6 KURU PATIENTS:

Specimen I is before first injection of BAL in all cases.

Specimens are in trace-metal free aluminum-topped bottles which have been specially trace-metal free washed and they are rubber-washed.

NAME	SEX	AGE	NUMBER OF BOTTLES	
Amakiora	F	6	3	URINE I
			3	URINE II
			2	URINE III
			1	URINE IV
			2	URINE V
Oma	M	6	1	URINE I
			1	URINE II
			3	URINE III
Yosetme	M	6	3	URINE I
			3	URINE II
Tuka	F	11	3	URINE I
			3	URINE II
Seribe	F	12	3	URINE I
			3	URINE II
			3	URINE III
Ake	M	14	3	URINE I
			3	URINE II
			3	URINE III

FIXED VISCERAL TISSUES ON KURU PATIENTS: Brains still hardening--to follow in later shipment.

Waruye	(HCHO and Zenkers fixed)	male, 8 years old
Inare	(only HCHO fixed)	female, 30 years old

DECEMBER 5, 1957
[NIH, BETHESDA, MARYLAND]

GAJDUSEK
OKAPA VIA KAINANTU
NEW GUINEA

BLOOD FINE TASIKE BRAIN GOOD ISAISI FAIR ATOWA POOR COULD YOU FIX
BRAINS FOR THREE WEEKS BEFORE SHIPPING STOP SHORT CABLE ADDRESS
SMADEL INSTITUTES STOP

SMADEL

MEMORANDUM

To: Dr. Carl Baker

Date: December 6, 1957

From: Richard L. Masland, M.D.
Assistant Director, NINDB

Subject: Trace Metal Studies in Respect to Kuru

At the suggestion of Dr. Cantoni, I had a telephone conversation with Dr. Bert Vallee. Dr. Cantoni had indicated that the latter was the most experienced student and investigator in this area. I described for Dr. Vallee the problem of kuru, pointing out that the distribution and character of the disability lent support to the thesis that this might be an intoxication or deficiency disease, but that we had no specific leads of what the nature of the deficiency might be. I then inquired as to whether he or members of his organization might consider it worthwhile to undertake analyses of the neural tissue which we now have available.

Dr. Vallee replied in the negative. He gave as an example his experiences with the single element, magnesium. Animals deprived of magnesium for considerable periods of time will still show normal levels of this element in the tissues, when these tissues are analyzed in the usual fashion. In order to demonstrate the irregularities which occur under conditions of magnesium intoxication or deprivation, it is necessary to fractionate the neural tissue--that is, to separate the glial cells from the interstitial tissues and from the mitochondria. When this extremely tedious work is completed, then very significant changes in the distribution of this element can be demonstrated. Dr. Vallee cited this to indicate the extreme complexities of the problem of doing trace metal analyses, pointing out that in this instance where we do not suspect any single element, it would be almost a life work to carry out significant studies. Dr. Vallee further indicated that, although he has had repeated requests for such studies, in each instance where effort of this sort have been made, a great deal of time has been spent collecting data which has subsequently been found valueless. It was his recommendation that these difficult and timeconsuming studies should not be undertaken unless there is some specific clue as to the particular element requiring analysis.

In the light of the above recommendations, I am hesitant to make further efforts to obtain these analyses until Dr. Gajdusek has returned and we can confer with him about it. With Dr. Klatzo, I have examined the three specimens which we recently received in plastic bags. We have reported on the state of preservation of these specimens, and they will be retained intact by Dr. Klatzo in the proper containers until such time as a decision as to their disposition can be made by Dr. Gajdusek.

/s/ R.L.M

Richard L. Masland, M.D.

Okapa Patrol Post
via Kainantu, E.H.
Territory of Papua and New Guinea
December 7, 1957

Dr. J.E. Smadel, Assoc. Director
National Institutes of Health
Bethesda, Maryland

Dear Joe,

On re-reading Bentley Glass' summary to "Copper Metabolism: a Symposium on Animal, Plant and Soil Relationships", sponsored by the McCallum Pratt Institute of the Johns Hopkins University and edited by William D. McElroy and Bentley Glass, The Johns Hopkins Press, Baltimore, 1950, I am more than ever impressed that I may have been very naive in expecting trace metal studies of a crude nature to reveal a trace metal-induced illness such as Kuru has many signs of being. Thus, the copper, iron and molybdenum interrelationships are so acute and so complex, that relative concentrations of each can determine excess or deficiency state of one--and absolute values for one alone could be most misleading.

Why do I keep suspecting metals? Well, Wilson's disease is still the nearest 'ringer' for Kuru, and it is a heredofamilial copper-protein complex deficiency, if I recall recent literature correctly. Secondly, I now am cognizant of the fact that ascorbic acid oxidase diamine are also copper containing. We already know of heredofamilial biochemical defects occasioned by disturbances in tyrosine, phenylalanine systems (phenylpyruvic oligophrenia to be specific). Finally, all the recent work on psychoses (schizophrenia) and other CNS ailments being associated with reactions which are specific for copper-proteins lets one think along these lines further. When one hunts for toxic basal gangliar or cerebellar damaging agents, one is left with mercury, copper, manganese, as far as I can find out thus far. Animal deficiency diseases involving ataxias have been traced to trace metal deficiencies (and here the copper molybdenum complex interaction story has come to the fore). All these threads of thought keep bringing me back to the trace elements and copper in particular. Others may act antagonistically or synergistically to copper...the molybdenum interaction is the only one I have thus far dug up.

Now, our study of Fore diet has revealed an immense consumption of ascorbic acid. Sweet potato staple is very high in ascorbic acid. This has led me to wonder, a rather naive and rash wonder, I suspect, whether excessive ascorbic acid, tyrosine, or some other normal metabolite intake might not put demands upon enzyme systems in excess of those which a normal, or somewhat low, supply of the trace metals required can supply. Glass' statement: "Moreover, ascorbic acid oxidase, tyrosinase, and all other copper enzymes become irreversibly inactivated during the course of the reactions they catalyze"...this brings this possibility even further to mind. Thus, I am now wondering whether copper enzymes may not have as a substrate some normally present product, either in excess in Fore diet or not handled by a marginal

copper supply, and this metabolite in turn does the toxic damage. Allowing for the hundreds of other possibilities, this sort of thinking makes it apparent that simple hunt for excess of some trace metal is not enough. For this reason I wonder how we can manage to investigate such matters as serum ascorbic acid levels in our patients. Serum phenylalanine and phenylpyruvic acid--can you get any of these worked out on blood specimens we send you? I am doing all in my power to keep them refrigerated from here to you and succeeding to some extent. Could you check for the usual FeCl_3 -test (I think) for phenylpyruvic acid in the urines you are receiving? Could your biochemists get into the serum for any lead? Or, is the age of the specimens on arrival such that these analyses are hopelessly delayed and useless already. I only mention all this for it seems apparent that biochemistry does not work as simply as it would have to, were we to have a copper or molybdenum excess staring us in the face by microelement studies. These must be done; they may prove the matter to be far simpler than I now fear. But, the more likely thing is one of these more complex effects. When I return I certainly hope to be able to pursue such a line, but the thought came to me that there is some possibility the NIH or NINDB groups might get a lead from appropriate specimens sent now.

I shall send some pure hydrochloric acid preserved twenty-four hour urine collections for amino acid studies. Can you handle these? BAL (Dimercaprol) has now been used on ten further cases and to no apparent effect. Let us not dismiss trace elements, but think in terms of their role, rather than in terms of toxic amounts thereof.

Since writing page 1 of this letter, your letter of Nov. 21 has arrived. I shall answer all it brings up:

1. The position with NIH and NINDB is excellent and fully satisfactory and I shall do my best to get there early. At the moment the Australian Adelaide University team is to be here in a few days, is to stay for only a month, and is to get very little done unless I keep patients together and on hand for them, for it is ever more difficult to bring patients into our Center for study and to persuade them out of their bush hamlets when I find them there on case-hunting patrols. Once they are under way, I am off.

2. Enclosed are protocols on the last six cases BAL treated, on whom urine specimens have gone off, as summarized in my last letter to you. These document time of urine collections and their volumes.

3. Zinc has been added to mercury and copper as a known basal-ganglia-ataxia producing chronic toxin and I urge that zinc, mercury and manganese poisoning be ruled in or out definitively on the bloods, CSF's and these urines, if at all possible.

4. Deficiency possibilities are going to be harder to track down, I fear. Perhaps copper, molybdenum, manganese and zinc--certainly Cu is "essential" and the others probably are. Levels might give a hint in this direction, but if it is a "relative" deficiency, i.e. relative to some other metal or to the supply of some metabolite, it will be much more difficult to track down.

5. The twelve enlarged prints are here. They are for the German article which I have rewritten and will send off in revised form with the prints. It brings the Kuru series up to two hundred cases and includes many new highlights of epidemiology. The German journal has accepted the article and I hope will not mind the revisions. The journal is Klinische Wochenschrift.

6. The NEJM article is fully satisfactory and I thank you, Joe, for all the help. I had not seen it until you sent the pages. The Medical Journal of Australia article is out and except for a few misprints and a rather poor quality of photographic reproduction, is also a very satisfactory article. The journal editor did a mighty job in making all the changes and revisions to bring it up to the 154 case level and to add all the newer findings which I rushed in the last minute. We had to keep it as up to date as TIME, at least. I am satisfied with what they did.

7. Graeme Robertson's path reports on the three brains he had been sent had never reached me. Late in September or early October, while I was crossing the island on foot after leaving the Kukukuku peoples, the TIME reporter arrived and to Vin's horror he showed Vin the path reports which we had never received. Although I have attempted to deal directly with all our collaborators and have done so, for nothing short of that can mean a thing, for we alone know what the specimens are we are sending out, prestige and publicity considerations have brought in numerous "intermediaries" at many stages. Thus, in the trace metal reports, elaborate studies I had collected for, arranged for and requested were lodged in Moresby and Melbourne files unknown to us, while those who did them could not have a clue in the world as to what the specimens were they had studied, or exactly how they had been collected. I found these reports by chance in going over files in Moresby. The same had happened to Graeme Robertson's original path reports. Yes, Joe, Australian feelings have been hurt by not having everything on kuru studied in their hands. The lead article in their journal, an editorial on Kuru, proves that amply. Since they may be better set up for solving some of the trace metal excesses or deficiency possibilities than anywhere else, I certainly hope that they may be able to turn up some leads as to pathogenesis. However, all collaborators we have had are fully documented in reports as they come out, and joint studies are all based on extensive correspondence. I feel that everyone concerned has been amply informed at every stage. Any objections you have received stem from dislike in not being "exclusively" involved in the Kuru study, to the exclusion of all collaborators, who, it seems, are looked upon not as coworkers seeking knowledge, but as competitors.

8. Mrs. Beyersdorfer has sent a fine report of the kuru film file and I only hope that further films keep arriving safely. I have what I hope are excellent follow-up pictures on many cases filmed in their early stages of illness. Furthermore, if the film now at Lae gets up here soon, I shall make cine films just before leaving of many cases that have been cine-documented well in the early phases of their illness and are now terminal. Please urge her to return to Lucy Hamilton the Kodachrome originals after prints and copies

- 4 -

are made for our file. I sent only a few of Lucy's best, so that we might have the advantage of these on hand. I myself will have a Kodachrome file of some thousand pictures to add to Kuru documentation. I am sending a few of Jack Baker's Kodachromes which do not duplicate material I have been able to photograph. These originals should also be returned to Jack at the address I send with the slides. Thank you and thank Mrs. Beyersdorfer for the immense job of film filing and processing. I think if they are all kept together, that I shall be able to identify and describe every shot.

A merry Christmas and a happy New Year.

Sincerely,

/S/

Carleton

Okapa Patrol Post
via Kainantu, E.H.
New Guinea
December 19, 1957

Dear Joe,

The Australian team is here with a two thousand pound grant for Kuru study, but the first two, Dr. Donald Simpson, Professor of Neurosurgery from Adelaide, and Dr. Harry Lander, in medicine and toxicology at Adelaide, must leave after a brief ten days of looking over our "kuru menagerie". They are excited, impressed, and having come to prove it a toxin have swallowed hook, line-and sinker our genetic evidence and are trying to dissuade me from my current toxic stand. Professor Robson and old Dr. Cleland of Adelaide are due on December 26 or thereabouts, and since their program will start in a shambles if I do not stay--perhaps I am over-exaggerating my importance as a cog in a wheel--I have again postponed my departure pending their arrival and moving in. They too will be limited in time, but they may have six weeks or so.

Simpson has given me a good deal of neurological training, corrected my numerous neurological errors, pointed out my neurological blunders and oversights, and straightened out all the neurological pedantry of the Kuru situation with me. I am pleased to see that we were not as far out as we might well have been. In general, however, I find Vin and I are winning point by point in the "re-description of Kuru", although Simpson has clearly shown that we have left misimpressions in our accounts thus far. Pyramidal damage can be detected; the clinical picture is more cerebellar than anything else. But, above all, it is a static and kinetic picture with repeated change depending upon emotional mood, upon environment and physiological state. Thus, even knee jerks can, during a single examination be very extremely marked, as with kinetic scoliosis, one time and disappear another; the nystagmoid eye jerking can approach true nystagmus one day and later that day have almost disappeared. Strabismus may occur in transient spasms or brief periods, and almost any reflex pattern, especially extensor plantars which we have now occasionally found from patellar and ankle clonus, pectoralis after tremor, to eyelid and orbicularis oris fibrillations, can come and go during one examination. Nothing in all this puts us a bit further ahead etiologically or pathogenetically. I still believe we have a strong heredofamilial, genetically determined predisposition to some as yet undetected environmental variable. That the variable may be an infectious agent is beginning to seem more and more possible in my mind. Thus, I beg that your neuropathologists get all the protozoological, spirochetal, leptospiral, fungal and viral histological studies and search done that they can. Toxoplasmosis was long in being discovered, and the Pneumocystic carinii stared pathologists in the face for generations before it was "seen".

Our case developing on the Papuan coast--and it is a certain case of rapidly advancing Kuru--is soon to be fatal, though he was never yet back in the Kuru region since its onset; we are keeping the patient at Kainantu. He got ill while working on the Papuan coast and was away from the furthest limit of the Kuru region for two months, at least, before the first subjectively evident ataxia appeared to him. Thus, Joe, toxic factors, if any must

be so subtle as to be hidden in the cloak of enzyme defect or intermediary metabolite, etc., I feel. Otherwise, this case and much more of our epidemiology becomes uninterpretable. Finally, if we are "missing the boat" this might be by excluding infectious possibilities too glibly. The diffuseness of the pathology from one point of view coupled with its specificity as a well ordered "syndrome", hitting only certain systems of cells and not others; all this is still a possibility. Protozoas, viruses, trypanosomes, Borelia, Treponemes, these are all in my mind at the moment. How else can the patients "take the illness out of the region with them", when either in the earliest stages or before the disease has developed, and still progress or get ill in "kuru-free" regions, progress to fatal deterioration? Enough.

Shipping with this letter: cine films, still films (all undeveloped and thus warn everyone not to 'look' at the films until both cine and still are developed); two brains and other tissues from good Kuru cases:

WARUYE M-6 years: in trace metal free 5% formal saline of limited volume and thus perhaps not adequately fixed. Why not fix it further?

INARE F-30 years: in regular pathological 10% formal saline in adequate volume and probably well fixed.

Pituitaries insellas, peripheral nerves and cord specimens are in the bottles or packed in the plastic sacks with the brains...do not lose them in unpacking, please.

Enclosed are lists of other specimens off in recent shipments. Yes, I am leaving in spite of repeated delays. When Professor Robson arrives in a week or so, I am off.

Sincerely,

/S/ Carleton

Cine films 16mm in kodachrome taken on Paillard Bolex Camera supplied to the kuru research by the National Institutes of Health, Bethesda, Md. These are all on Australian manufactured cine kodachrome-daylight type, for which processing has been paid in advance. All exposed at 24 frames per second and without filters.

Cine Film No. 25: Exposed December 15, 1957

24 frames/second. No filter. Kodachrome-daylight type.

Moke-Pintogori:

Kumpa	M-13 years old	} Three kuru cases, all ambulatory.
Amakiora	F- 6 years old	
Yosetme	M- 6 years old	

Feet and toes and patellar clonus on standing of Kumpa; feet of Yosetme.

Cine Film No. 24: Exposed December 16, 1957

24 frames/second. No filter. Kodachrome-daylight type.

Moke-Pintogori Kuru Hospital patients seated from right to left:

Tawasa	F-14 years old
Asisi	M-12 years old
Yosetme	M- 6 years old
Ake	M-14 years old
Amakiora	F- 6 years old
Seribe	F-12 years old
Awani	F-30 years old
Aoga	F-10 years old

Final scene of patients being brought back to Kuru ward.

Cine Film No. 25: Exposed December 17, 1957

24 frames/second. No filter. Kodachrome-daylight type.

December 17, 1957:

Okapa Village...2000-3000 feet below "Okapa Patrol Post" showing views of region, and Kuru patients

Tete (light skinned)
Noka (dark skinned)
Kasiwari (man)

December 19, 1957

Kuru patient Tageiro at Anumpa Village. Examined by Dr. Donald Simpson, neurosurgeon of Adelaide.

Post mortem specimens in trace metal-free bottles kept in refrigerator.

Yani M-4-5 years old: Autopsy performed on December 13, 1957, about
4-6 hours post mortem, liver, kidney and spleen.

Auwatnefa F-30 years old: Autopsy performed about 12 hours post mortem on
December 15, 1957, liver, bile, kidney, spleen,
skeletal muscle and piece of cervical spinal cord
in one bottle.

These are the last trace metal-free specimens of tissues we are apt to get from autopsy work. Thus, please see that everything possible is done on them, if possible from heavy metals, to arsenic and rare earths. Should their condition be adequate, as the result of refrigeration and prompt receipt, for any other studies (creatine, creatinine, lipoids, etc.) please see if these also may be done. We are, obviously, at wit's end trying to get some lead in metabolic defect or toxic accumulation.

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
December 24, 1957

Dr. J.E. Smadel, Associate Director
National Institutes of Health
Bethesda, Maryland, U.S.A.

Dear Joe,

Enclosed is a full manuscript, including associated correspondence of my revised article in press in *Klinische Wochenschrift*. This is a rather more definitive paper than the American and Australian preliminary note and it also corrects a few previous errors and misconceptions, as well as bringing case figures up to the two hundred mark. Our "cases" for this year are now approaching 250!

I have seen the vanguard of the Australian team in and out. Lander and Simpson were refreshing, although brief coworkers. In a few days Robson and elderly Prof. Cleland are to arrive. I shall turn over records and data to them and then be off. However, the mass of records, data, and full correspondence files are now being packaged. Today I am sending the full case records of our first fifty deaths, along with massive correspondence, laboratory data and epidemiological files, off to you via "Convert to U.S. Government Bill of Lading" shipment. These should be in your hands as soon as this letter arrives or earlier. Since the entire study in the U.S. depends upon the successful receipt of this first stack of records and of the next shipment which will go off one week later, along with my departure, I am most anxious to know of their safe arrival. If you can let me know by the 7th January of the receipt of the large box of records by cable, you can still reach me here. I shall try to depart on that day.

Two brains are off to you, and when you acknowledge receipt of the first stack of records by cable, it would cheer us a good deal to know of the arrival and condition of these further brains. One additional brain is hardening and will be shipped off before I leave. However, we have given one to Prof. Sunderland of Melbourne, who visited us, and another of our posts, including the complete spinal cord, went off to Adelaide with Simpson who was just here with us. The Australians will certainly be after all the others they can get so those now en route and the one remaining may be the last. Vin and I, however, are still the only ones getting posts and collecting cases, and since so much of our hopes lie in the work going on at NIH, we shall do our best to route at least another one or two brains along with spinal cords--for it is now fully evident that paralysis and muscle fasciculation are present as late terminal phenomena and that cord damage as a late development is probably certain.

I am sending out further blood specimens and before I leave I shall send out finger nails and hair from controls and Kuru patients for AS and trace metal studies. We rounded up a stack of finger nails on patients and controls for Harry Lander of Adelaide for AS studies, which he is doing, but since hair and finger nails are important in many metal toxicities, we shall send these off during the next few days. Bloods and urines, etc. will go off during the next week, and further specimens will go off after my departure. In addition, vast serum files in Melbourne for study of an abnormal serum globulin found even in normal Fore natives, and for other studies,

are being sent off to you by Lois Larkin for me. Thus, within about two weeks the last of the stacks of records and specimens should be posted and I shall be bound for Washington.

Kuru is obviously more important than all expectations. That it is a new disease is certain, that it offers astonishment, intrigue and imagination to the neurophysiologist (Prof. Eccles) and neurosurgeon (Simpson) beyond anything they have seen in their careers, we had expected--but this is interesting confirmation of the suspicions we had, that it is something which modern medicine cannot afford to pass by as a simple medical oddity--there is too much chance here for real advances in our understanding of human physiology and disease if we can "crack" kuru, genetic or otherwise.

Endocrine possibilities must be pursued. Pregnancy does seem to retard the disease and it seems to progress more rapidly shortly after parturition. The adult sex ratio and a suggestion of more rapid deterioration while on stilbesterol therapy all point this way. Thus, 11 oxy steroid and 17 ketosteroid analyses on the urines we are sending seem in order. Can they be done on the HCl preserved 24-hour specimens? How about other hormone possibilities?

Protozoan parasite possibilities and errors of intermediary metabolism are all in the forefront of our attention. In the former case, only the pathologists and parasitologists can give us a lead. In the latter, we would suggest that some abnormal genetically determined pathway of steroid or estrogen or other sex hormone metabolism may be involved.

Enough for now.

Sincerely,

(S)

Carleton

69a enclosure

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
December 11, 1957

Editor-in-Chief
KLINISCHE WOCHENSCHRIFT
Springer Verlag
Heidelberg, Baden
Germany

Dear Sir:

I am sorry for the long delay in returning to you the enclosed card authorizing publication of our Kuru paper. In so doing, I am taking the opportunity of submitting a somewhat revised and corrected manuscript from that which you have now in your hands. Kuru investigation has been proceeding so rapidly that it has been wise to make these changes and additions. Furthermore, we have now had our preliminary reports published in the United States and in Australia and it is certainly in our interests and those of your Journal and of your medical-scientific readers to revise the story up-to-date and to bring in additional material not yet covered by our American and Australian preliminary reports. For this reason we beg that you use this revised version of the paper, which brings our study up through our first 200 Kuru studied cases.

If the article is to be published in German translation and if you have already submitted it to your scientific translator, we believe that he will find very few changes necessary and only small additions here and there. Should this be the case--that is, should it already have been translated--I am enclosing with the new, revised and retyped manuscript, a carbon copy of the old, original manuscript submitted to you on which all changes and revisions have been marked. This could be used by the translator in locating all such changes, additions and revisions, and thus simplify his task. If no translation has yet been made--or if, of course, the article is to appear in its original English version--then this corrected carbon copy can be destroyed as can your first original manuscript which is now to be replaced by this corrected, up-to-date and retyped version.

I am sorry to give you these editorial problems. However, we have had rather unfortunate world-wide publicity in the lay press given to Kuru and our work and it is certainly essential that the medical literature be at least as up-to-date and accurate as the newspapers.

Enclosed also are twelve illustrations many or all of which we hope you can use. Appropriate captions for these are included on an accompanying sheet. I believe that you have already received a copy of the map locating the Kuru region to be used as the first figure in the paper. This was to have been mailed from Melbourne to you some time ago. If not, another copy

is enclosed herewith. I expect that you will have it redrawn with appropriate German spellings, etc. May I point out that Mt. Michael is spelled incorrectly on the map, and should be Mt. Michael (not Mt. Micheal)?

Finally, I am enclosing a set of Kodachrome slides; appropriate legends for these are also enclosed on an accompanying sheet. It is our hope that you may consider some worthy of color reproduction in the Journal. If not, perhaps you may find it worth while to have black and white negatives made of some of them and include them as black and white pictures. In any event, please preserve all of these slides for me and return them to me when you have completed your use of them.

The only outstanding item in this paper is the second map, locating the Kuru region and the tribal-linguistic groups more accurately. This is an important feature of the paper and I hope to get it into your hands shortly.

Our work here at Okapa is to be called to a halt temporarily and in January or February I hope to be passing through Heidelberg en route back to the United States. I believe it is best to save any proof correcting and editorial comment until such time as I appear in late January or February in your office. Shortly thereafter, my address shall be:

c/o Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland, U.S.A.

I thank you for your kind editorial assistance and patience.

Sincerely,

D. Carleton Gajdusek, M.D.



INVESTIGATION INTO THE PATHOGENESIS OF KURU

Clinical, Pathological and Epidemiological Study of a
Chronic Progressive Degenerative Disease of the Central
Nervous System Reaching "Epidemic" Proportions Among
Natives of the Eastern Highlands of New Guinea

D. C. Gajdusek¹

and

V. Zigas²

1 Aided by a grant from the National Foundation for Infantile Paralysis.

2 District Medical Officer, Department of Public Health, Territory of Papua and New Guinea.

In early March 1957, the two authors initiated in a mountain-dissected region of the Eastern Highlands of the Australian Trust Territory of New Guinea an intensive study of a neurological disease syndrome new to Western Medicine and clinically akin to the chronic progressive heredofamilial degenerative disorders of the central nervous system, particularly the cerebellar and spinal ataxias and the degenerations involving the corpus striatum, and to certain chronic poisonings, especially that with manganese. The disorder affects exclusively the Fore people and their immediate tribal neighbors, and among those Melanesian Highland natives it has attained an extraordinarily high incidence, accounting in recent years for almost half of the deaths that occur in their communities. We have presented elsewhere details of our initial discovery and description of this disease (1,2). In this report we shall review the clinical and pathological findings obtained from an intensive investigation of our first 200 cases of this disease and our epidemiological observations of these cases and of an additional 600 cases of kuru which we have been able to document.

Kuru, as the disease is known by the Fore, is a word also used by them to designate the trembling associated with fear or cold. Among the Kimi people the disease is called Uruna.

Geographical Distribution

Kuru has been observed only in a mountainous region in the Eastern Highlands of the Australian Trust Territory of New Guinea south and east of Mt. Michael (elevation 12,500 feet) and some 30 miles southwest of Kainantu where the homeland of the Fore Linguistic and Cultural Group is located. These people and the tribes which surround them have only been pacified during the past five years and intertribal and inter-village warfare, ritual killings, sorcery and cannibalism, which included the eating of many of those who died, have all been discouraged by the government. However, remnants of warfare and cannibalism still survive and sorcery and ritual killings often in reprisal for kuru magic remain the dominant administrative problem in the area. The Kukukuku-type people who border the Fore people on the southeast along the Lamari River remain uncontrolled and their rugged country is still incompletely explored. To the south the Fore are bordered by uninhabited forested ranges dropping from the Highland drainages of the Yani and Lamari Rivers to the lowland sago jungles, homeland of the Bird of Paradise. Here in the foothills to the New Guinea Highlands, the Yani and Lamari unite into the Subu (or lower Lamari) River. The Subu shores are inhabited by the Yar subgroup of the Pawaian Linguistic Group, who inhabit the Upper Purari River shores of Papua.

This region is administered from the Okapa Patrol Post which was established in 1954 and is in communication with Kainantu by wireless and by rough 40 miles of jeep road. This Patrol Post is situated in approximately the geographic and population center of the Fore people, some 1,000 in number, and from it a total of some 30,000 natives are censused. All cases of kuru have occurred in or adjacent to this Division of the Kainantu Sub-District of the Eastern Highlands and nowhere in Papua or New Guinea where continuous medical observation of native populaces has been in progress for over 20 years (i.e. in such places as Port Moresby, Lae, Madang, Bulolo, Wau, Goroka and Mt. Hagen) has a verified case of this disease occurred.

Within the region the disease is clearly one of the Fore people. Every Fore village and hamlet has a history of recent kuru deaths and very few are lacking a currently active case of kuru included in our kuru study series. The disease thus occurs in the entire region inhabited by the Fore Cultural and Linguistic Group and, in addition, extends into the neighboring linguistic and cultural groups of Auiana, Usurufa, Kanite, Keiagana, Iate, Kamano and Kimi peoples. Furthermore, a small group of 700 Iagaria people whose tribal lands are on the western slopes of Mt. Michael but who migrated to this region east of Mt. Michael several generations ago and have extensively intermarried with the Fore into whose territory they move, are also affected with kuru. In the areas administered from neighboring government centers of Lufa (west of Mt. Michael), Kainantu, Menyamy (to the southeast), and Kerema (on the Papuan coast), no kuru has developed. In the adjacent region administered from Henganofi, to the northwest, the disease has occurred only in those villages bordering on the kuru region in the Okapa administrative district. In each of the Fore neighboring groups kuru affects only the portion of the population immediately adjacent to the Fore. More remote settlements of these other peoples, who do not intermarry with the Fore, have not experienced kuru. Iate, Kanite and Usurufa groups are small populations, all portions of the land they occupy lying close to Fore kuru-affected populations and all of the villages of these small groups have a history of kuru. All of the Fore neighbors except the Kukukuku across the Lamari River and the Yar people of Pawaian stock from Papua are thus far known to have kuru in those settlements bordering on the Fore. The Kukukuku are separated from the Fore by the formidable barrier of the Lamari River and have no marriage contacts with Fore villages other than two recent marriages of Fore women into one Kukukuku hamlet. Ecologically, however, the Lamari forms no discontinuity and variations of terrain, elevation, vegetation and rainfall are greater within the Fore lands themselves than at any of the kuru-non-kuru boundaries. The Yar people to the south are separated from the Fore by three days of hard walking through dense forests and likewise have little marriage contact with the Fore-that which they have limited to one recent marriage with a Fore woman. However, they visit the Fore frequently and have recently adopted into the Yar village four Fore youngsters. It is of interest that during inter-tribal fighting, the Fore of Kasarai, the most southernly of the Fore villages, moved southward temporarily toward the Yar people to settle for over a decade at Abonai which is already in sago country, probably under 2000 feet elevation. While living here in sago jungles they still had cases of kuru deaths among their women.

The kuru area ranges from 3000 to 7000 feet in elevation and its mountainous terrain is dissected by broad, deep valleys. Most ranges are heavily forested on their summits and these forests abound down into the valleys in some places. Kunai grass covered slopes predominate, however, at the lower elevations. The Fore live both in settlements on these kunai slopes and also in small hamlets in the forests. Kuru follows them from the lowest and most open of their settlements to the highest forest-hidden hamlets.

The accompanying map (Figure 1) illustrates the location of the kuru region in New Guinea with respect to all places thus far mentioned in the text.

Insert Figure 1 here.

A more detailed map of the kuru affected region showing the extent of kuru within each linguistic and cultural group is presented below in the discussion of kuru epidemiology.

Historical Background

The first recorded entry of Europeans into the Fore region is the expedition in 1936 of Ted Ubank, a gold prospector. On this occasion large pine forests were discovered at Okapa which are now used as a source of seed for Highland forestation. In 1949 a Lutheran Mission was set up at Tarabo in the Keiagana Linguistic Area and when the government established its first patrol post, called Kumiawa, in the region in 1952 it selected the same site. In 1954 the administrative center was moved to the Moke-Pintogori region in the center of the Fore Linguistic and Cultural Group and incorrectly named the Okapa Patrol Post. Until the initiation of our Kuru Research Project, the Okapa Patrol Post was a seldom visited out-post from which 30,000 natives were censused and administered and in the entire region only two Europeans were resident: the missionary at Tarabo, and the government Patrol Officer.

Patrol officers noted kuru-referred to as skin guria in Pidgin English- in their patrol reports as early as 1953, and it soon became apparent to succeeding government officers in the region that "the shaking disease" was the major medical problem in the area. In 1951 and 1953 Dr. and Mrs. R.M. Berndt, doing anthropological and linguistic field work in the linguistic blocs of Kamano, Usurufa, Jate and Fore noted the illness among the Fore, Jate and Usurufa peoples (3). The disease was brought to the attention of one of us (V. Zigas) in 1955 and an effort was made to study it and determine its cause. Early in March 1957, the two authors joined forces and inaugurated an intensive study of kuru at Okapa. A special native materials hospital was quickly erected to house the kuru patients whom we assembled, and a laboratory and treatment room was built in which examinations and studies could be conducted. Jeep transport provided a means of sending specimens out to the airstrip at Kainantu from where they were flown for special studies to laboratories in Port Moresby, Australia, and the United States. The Kuru Research Centre which was thus set up subsequently proved to be located very close to the geographic and population center of the kuru region. Eighty-five kuru patients have been intensively studied here by clinical and laboratory investigations and therapeutic trials of numerous drugs have been conducted. In addition, case finding and epidemiological patrols were launched from this Centre to all parts of the kuru region and into the surrounding territory. On such patrols another 65 patients have been thoroughly studied in their village setting. The remaining 50 patients in our series of studied cases have not been fully examined and in some cases are documented as cases which have developed and died during our period of kuru study, having been seen only by our Native Medical Assistants. We have, in addition, operated a native hospital servicing the entire region administered from Okapa to which there have been over 1,000 admissions during the 6 months of kuru research. Here we have made a motion picture film of kuru showing its clinical progress from early ataxia to incapacitation and death and its prominent place in Fore culture and we continued to document in cine film the clinical progression of the illness in many of our patients.

Ethnographic Setting

The Fore and surrounding people are Melanesian natives in the throes of experiencing their first European contacts. Although most have seen Caucasians during the past 5 years, few had seen European women or children until our Centre was visited by European families. To these natives kuru, as is all disease, is the result of kuru sorcery magic and occupies a very significant place in the total fund of Fore sorcery. Kuru is worked upon its victims usually in response to some real or imagined wrong, such as failure to respond to courting overtures, and for this purpose the sorcerer, who may be any male member of the community, requires a portion of the victim's person, excreta, clothing or discarded food. Thus, faeces are most often used, but hair, skin from sweet potato eaten by the victim, a piece of the victim's "maro" (or bark skirt) are often employed. This material is carefully packaged in leaves and bark, tied with vine and placed partially submerged in a swamp. The sorcerer then visits this half-buried charm and shakes it each day until his victim commences to shake with the "shaking disease" kuru. Thereafter, the charm is left to decay in the swamp. Once started, kuru follows a relentlessly progressive course to death, and in most Fore communities one is told that it is never cured. However, in certain communities in which cures or recoveries are known, these are readily explained: 1) the sorcerer has relented, and has removed his charm, 2) the sorcerer has been discovered or revealed himself and bribed to hand over his charm to the kinsmen of the afflicted, 3) the sorcerer has been discovered, often by magical divination, and forced or bribed to execute counter-magic, and 4) the process of divination has been used to locate the site of implantation of the kuru charm and the charm has been thus discovered and destroyed. This divination in order to discover the site of burial of the kuru charm usually takes the form of collecting water from numerous springs and offering these to the patient. When the water from near the offending site is consumed, violent vomiting and retching ensues, and the location is thus established. The site may then be closely watched to note who approaches it for the purpose of visiting and shaking a charm. On the other hand, the village or hamlet to which the sorcerer belongs may be determined by roasting numerous small rats, each in a bamboo cylinder, over a cooking fire. Each beast is arbitrarily assigned representation of a community under suspicion. After cooking, the animals are opened and that animal with particular discoloration and changes in its viscera is taken as indicating the offending clan. Occasionally, bribery may then be resorted to in order to purchase the kuru-invoking charm. More usually, reprisal in the form of warfare, in the past, and ritual vendetta murder in the past and present are resorted to. Such reprisal usually takes the form of tukabu, a culturally dictated form of ambush on the first members of the offending clan to appear, or on a particular individual suspected of having worked the kuru magic in which the means of assault are formalized and fully prescribed by tradition: pounding of the humeri and femuri and of the renal areas with stones, pounding of the anterior neck with stones or wooden clubs, biting of the trachea until it is fractured, and crushing of the external genitalia with stones and clubs.

We have seen victims of tukabu after they have been so dealt with and succumbed and others who have been brought to us in severe distress from a recent tukabu attack which has been interrupted by the appearance of the victim's clansmen.

Thus, kuru accounts for more deaths than those of its immediate victims, for in the past, as at present, a considerable number of people are murdered in reprisal for having worked or being suspected of working kuru magic. In addition, kuru victims are often women with nursing infants, and upon the death of the mother such children usually die of malnutrition, for the Fore have not generally accepted the practice of transferring the infant to another nursing woman. Kuru magic is traditionally the property of the Fore people and those surrounding peoples who suffer from kuru attribute to the Fore or to their own men instructed by the Fore the sorcery responsible for kuru in members of their communities.

Clinical Picture

Kuru is remarkable for the uniformity of its symptomatology and clinical course. In fact, so unvaried is the clinical pattern that its stages are described by the natives in almost non-variant form throughout the kuru-affected region, and both the disease and descriptions of its phases have become part of the traditional magic lore of the Fore people. However, in the following account we will emphasize the variations in the clinical picture we have been able to observe.

The first symptom is locomotor ataxia, insidiously progressive and often noted by others before the patient himself is aware of it. About one-third of the patients report knee pains, headache, malaise, fever, cough or coryza, in order of decreasing frequency, as prodromal symptoms, but none report an acute incapacitating antecedent illness with emesis, stiff neck, convulsions, pareses, coma or even moderate interference with normal activities. None show signs of recent weight loss. Thus, antecedent acute infectious illness, severe enough to be recognized as meningoencephalitis or any other clinically diagnosable acute infectious disease is absent.

The ataxia becomes more marked with awkward placement of the feet and a swaying and weaving gait, and the patient tends to trip and stumble. He often describes this phase as "loose knees". If knee pain is reported associated with the onset, it rarely persists for more than a few weeks. As ataxia becomes progressively more severe, a distinctive tremor involving the trunk, extremities and head appears and this tremor is exaggerated when the patient attempts coordinated voluntary motor activities, is placed into any unstable posture, or when he is excited or apprehensive, fatigued or exhausted. Within one month of the onset both the ataxia and tremors are usually prominent but the patient generally continues a normally active life.

The tremor is usually of fine quality, irregular but approximately of two to three per second frequency and has the appearance of shivering. It largely subsides when the patient is sitting quietly relaxed and disappears in sleep, but generally tremors appear when the patient is emotionally stimulated and then become exaggerated upon muscular activity, particularly in those muscle groups placed under controlled motor response or required to maintain unstable posture. During the second to third month of illness, when tremors become more

severe and rather coarse in quality, they may interfere with eating and with fine motor skills involving hands or feet and a choreiform component may enter into the involuntary motor pattern. Some patients progress to wild, somewhat athetoid involuntary movements in addition to the tremors and choreiform jerks, and this is particularly noticeable when they try to arise to an erect from a recumbent or sitting posture. By this stage the patient is no longer able to walk without the support of a stick; yet he generally continues to perform his usual daily chores about the village and gardens. Most patients, however, can continue to walk with such support for only one or two months, and thereafter can no longer maintain their equilibrium unassisted. From that time the patient remains sedentary but still moderately well integrated in his native society, sitting outside the house and half-carried to attend pig feasts or other social functions. However, he invariably deteriorates rapidly until he can no longer balance, even in a sitting posture without being supported and thereafter is carried out of the low, dark, kunai grass house only for urination and defecation. In a short while, in this advanced stage of disease, reached in the usual village setting, the patient is no longer carried from the dark house, but left to lie indoors with fecal and urinary incontinence and rapidly developing decubitus ulcerations. Convergent strabismus is often present at this time. Until the patient can no longer maintain a sitting posture unaided, he usually can still bring food to his mouth and eat; but once he assumes decubitus he must be fed. This stage is brief, however, and the mute patient then rapidly succumbs to starvation, infected decubitus ulcerations, occasional accidental burns from the house fire, and secondary static bronchopneumonia. During this entire course the patient remains afebrile unless fever accompanies a transient intercurrent infection.

Speech and intelligence are normal in the early stages of the disease, but dysarthria appears in the second to fourth month and becomes more marked as the disease progresses. At the time the patient is no longer able to walk without extensive bilateral support, speech is usually extremely blurred and slurred, yet it is still intelligible, and verbal responses, although much slowed, reveal good orientation and are usually appropriate. Even at an advanced stage of incapacitation the mute patient, who only occasionally groans, may still behave intelligently to requests with a feeble motor response after much verbal urging.

As the disease progresses, but still in the early months of illness, a marked emotionalism appears with inappropriate excessive laughter and slowly relaxed smile or paroxysmal hilarity alternating at times with moods of depression and, occasionally, of moderately belligerent and aggressive behavior. This moodiness, more usually that of excessive euphoria than of depression, settled later into a gradual pattern of withdrawal with an immobile facies, less mask-like than that of classical Parkinsonism, often present and with a flexed posture characteristic of the disease. In those few patients who are adult males, a dejected, somewhat morose and somber facies is usual, whereas, the usual patients, children and women, tend to be happy, even euphoric, in mood and appearance. In the native village the disease usually runs its course in 6 to 9 months and rarely lasts over one year. Occasionally, cases die within three to six months of the onset. A few cases, particularly in older women, run a more slowly progressive course to death in one to two years or longer.

Thus far, 14 of our 200 studied cases have apparently recovered. Of these, we have only studied and examined 6 actually during attacks of "kuru" and for the other 8 we have accepted what appear to be reliable anamnestic data to the effect that they have recently had typical early kuru which has subsided. Of the 6 fully examined cases, now apparently recovered, only three were considered unquestionable kuru cases while we first examined them. The remaining 3 have been so mild or early in the ataxia and tremors that we have always been in doubt about accepting the native diagnosis in those cases. The three moderately advanced cases, however, had marked ataxia, incoordination and tremors and emotionalism characteristic of moderately severe kuru and in their case, at least, we must concede that they are observed kuru "recoveries". All three were in adults of somewhat hysterical temperament--two women and one young man. It is our current hypothesis that the illness is uniformly fatal and that the recoveries which we have documented and the six we have observed are cases of hysterical mimicry of the ataxia and the dramatic involuntary tremors and incoordination of kuru. Since the kuru pattern occupies a very significant place in current Fore culture wherein it is believed to be a purely sorcery-induced malady, and where all recoveries are attributed to counter-sorcery, or removal of the kuru-inducing charm, it would not be surprising to find it a pattern for occasional hysterical mimicry. In this connection it is of interest to note that R.M. Berndt has described an hysterical shivering and shaking occurring in men, women and children as a manifestation of a "cargo" movement in certain linguistic groups in the New Guinea Highlands (4).

The course of the disease is usually unrelentingly progressive with continuous and uninterrupted deterioration. However, a rare case with remission and exacerbation has been recorded. One woman gives a history, verified by interviews with others in her village, of having had typical early kuru some 15-17 years ago which lasted several months after the delivery of her first child and then subsided. Again, some 12-15 years ago, just after the birth of her second child, she had kuru with complete remission after a few months of mild tremors and ataxia, and now, for a third time, just after her sixth child has been born, kuru has developed. This third attack is a typical case of moderately advanced kuru now in its third month of progression, and showing no signs suggestive of remission. A second, moderately severe case in a woman of 25 years, is reported to be in its third exacerbation, having completely remitted twice (once 15-18 months ago and a second time 6 months ago) for periods of several months after having progressed to the stage of such tremors and ataxia that a stick was required for walking. The latter case appears now to be rapidly advancing and we believe it will soon be fatal.

In addition to these rare recoveries and remissions we have found two atypical cases of "kuru" which are already of several years' duration and which regularly appear and remit with the onset and termination of the patient's menstrual periods. Whether this periodic non-malignant illness and the cases of apparent recovery are examples of kuru incompletely expressed--formes frustas of kuru--which may offer valuable clues to its pathogenesis or whether they are distinct nosological entities remains an unsolved problem.

Kuru does not interfere with normal pregnancy. Many of our kuru patients are pregnant and four have delivered normal children while suffering from moderately advanced disease. We have recorded many cases of normal pregnancies and of deliveries of normal infants even in very advanced and incapacitating stages of the disease. Other cases have died before term without miscarrying before death. However, when a mother dies of kuru leaving a small suckling

infant, the child frequently dies of malnutrition since no other nursing woman takes over care of the infant.

Pregnancy may have a significant effect on the progression of kuru. Thus, we have frequently noted that our kuru patients are often pregnant mothers, or mothers with young nursing infants, and that during their pregnancy the illness is usually static, their condition tending to deteriorate rapidly during the few months after parturition while they are nursing. This situation has not been investigated critically enough to have been unquestionably verified, but it is a phenomenon sufficiently frequent to have attracted our attention over the past year of observation of kuru cases.

A remarkable aspect of kuru as it is met in the native communities is the extraordinary good spirited fatalism with which the patient and, in general, his relatives accept the disease. Patients know they are to die; they have observed the terminal incapacitating stages of the disease in others, and, yet, discuss the matter of their advancing illness freely and without apparent anxiety. They will laugh at their own stumbling gait and falls, their clumsiness, inability to get food into their mouths, and their exaggerated involuntary movements, and their kinsmen will join them. The family members live with the dying patient; siblings sleep closely huddled to their brother or sister in decubitus; parents sleep with their kuru-incapacitated child cuddled to them, and a husband will patiently lie beside his terminal uncommunicative, incontinent, foul-smelling spouse. They may abandon at an early stage such supportive measures as feeding and washing and bringing the patient out into the sunlight, but they never cease to give strong emotional support and security to the patient who, as have they, has accepted the inevitable fact of impending death from the onset of the illness with equanimity. Thus, the emotionalism and euphoria of kuru is supplemented by a security engendered from certain knowledge that one is accepted by his villagers as an unfortunate victim of kuru sorcery, whom they will not desert before death claims him. The vengeful search for the offending sorcerer, which is often the primary concern of the patient's kinsmen, is a source of further emotional support.

PHYSICAL FINDINGS

In early stages of kuru, physical examination reveals no systemic abnormalities other than those referable to the central nervous system. There is no fever except for that associated with inevitable occasional intercurrent infections. Nutrition is generally excellent and there is no muscular atrophy. Cardiovascular, respiratory, gastrointestinal, hematopoietic, genitourinary and endocrine systems are normal. Examination of the abdomen is negative and there is no hepatomegaly or splenomegaly. There is no lymphadenopathy. The skin and m cosa are clear; there is no nanthem or exanthem. No heavy metal lines or abnormal pigmentation are seen on the gums or buccal mucosa, except for the bluish-gray plaques opposite the line of dental occlusion seen in most natives of this region. Until late in the illness there is no muscular weakness or paralysis and no rigidity or spasm and, although in advanced stages, severe but inconstant muscular spasm and intermittant resistance to passive motion of the extremities appears, muscular contractures are very late in developing, in spite of the predominantly flexed posture which the patient generally assumes. In the terminal stages muscular atrophy becomes pronounced and some paresis or paralysis may develop.

The earliest sign of the disease is the slight ataxia often noted by the patient or his villagers before we are able to convince ourselves of its existence. The tremors, next to appear, are characteristic in that they appear to be closely associated with those muscle groups called upon to maintain any given posture against gravity. Thus, the muscles of feet and legs especially show exaggeration of this tremor when the patient is trying to execute a Romberg test or to stand on one foot. When executing finger to nose test, excessive tremors of the outstretched arm and hand are evident and these persist until the finger comes to rest on the nose of face where it is stabilized and supported. Some patients actually link the opposing index fingers together or press the fingers firmly together when they meet to control these tremors. The tremors can be considerably minimized or even occasionally abolished by supporting the trembling patient with firm and extensive anti-gravity support. Thus, one small boy with kuru who trembled violently when trying to sit or stand alone, had discovered a means of almost completely controlling his involuntary movements by remaining inactive in a flexed, fetal posture, cuddled closely into his mother's lap. His responsive mother held him thus completely supported throughout the day. His kuru tremors would only appear when he was removed from this extensive maternal anti-gravity support. By cuddling young, violently trembling patients tightly in our arms and restraining their heads and extremities against our body, we can succeed in almost totally abolishing their tremors.

Sensory examination appears normal. Although few patients have cooperated sufficiently through the barrier of language and culture, which we have slowly managed to surmount, we have found light touch, temperature, pain, vibration and position sense normal in a sufficient number of our moderately severe patients to convince ourselves that disturbances in sensation do not exist in the first few months of the disease, at least. Examination of the eyes reveals no abnormalities other than a convergent strabismus which first appears late in the illness. Vision is normal. Extraocular movements retain their normal range even when marked strabismus develops. When severe tremors are present, the patient has difficulty in maintaining a fixed gaze and his glance tends to shift about rapidly and irregularly. Nystagmus is absent and the pupils react normally to light and to accommodation. Blinking frequency is diminished in many patients. Funduscopy reveals no papilledema, exudate or hemorrhages, optic atrophy or macular degeneration or other abnormality. There is no greenish-yellow pigmentation at the sclero-corneal border (Kayser-Fleischer rings). Certain patients who are already sedentary and who remain indoors in the dark huts show a peculiar twitching, clonic movement of the eyelids and eyebrows when they try to keep their eyes open to the light of out-of-doors and, rarely, an advanced case shows a unilateral partial ptosis.

Cranial nerve function remains intact. Hearing remains normal. Emotionalism and intellectual slowing have been fully discussed above, together with progressive dysarthria. Slight disturbances in articulation may appear while the patient is still ambulatory, but marked dysarthria and, later, dysphasia are present in all advanced cases. The tongue is protruded and deviated normally and shows no fibrillation or tremors, but if carefully observed in the late stage of illness, quick shock-like jerking movements of the protruded tongue are noted. In late stages of the disease, drooling of saliva is common and some patients appear to have considerable difficulty in opening their mouths or protruding their tongues, as they likewise do, in such advanced disease, in directing and

focusing their gaze. In such patients, it is impossible to perform an adequate sensory examination or to evaluate fully their state of awareness and orientation.

The pattern of deep tendon reflexes and of cutaneous reflexes remains normal in most patients, although some patients reveal moderately hypoactive responses and others moderately hyperactive reflexes. Often, particularly in advanced disease, an unsustained but 5-to-10 times repetitive ankle clonus is found, and, more rarely, a sustained clonus, sometimes accompanied by unsustained patellar clonus. Normal deep tendon jerks usually pass to hyperactive responses and then become hypoactive in the terminal stages of kuru. In the stage of hyperactive responses a repetitive ankle and knee jerk and a pectoralis after tremor are noted. Abdominal reflexes frequently disappear as the illness advances. Cremasteric reflexes in male patients remain active. No other reflex abnormalities are usually seen. Signs of pyramidal tract damage may be absent until late in the disease, and plantar responses are usually flexor in type, even in the terminal stages of the illness, although occasionally, often transient, extensor plantar responses are obtained in advanced cases.

Cerebellar function tests reveal that the Rhomberg sign is present after the disease has progressed for a few months, but earlier, we have noted that the patients first lose the ability to stand on one foot with eyes closed and, subsequently, they cannot maintain balance on one foot even with their eyes open. Cerebellar function tests tend to exaggerate the irregular tremors and choreiform component in their involuntary jerks; at times even a somewhat athetoid pattern appears in the extremities of patients attempting these tests in the more advanced stages of the disease. Usually the response to the heel-shin test is more extensively disturbed than are the responses to finger-to-finger and finger-to-nose tests, and difficulty with the heel-shin test tends to appear earlier than that in the upper extremities. This difficulty includes a wide amplitude tremor of foot and leg in attempting to place the heel on the tibial tuberosity, difficulty in initiating and in maintaining continuous smooth progression of the heel down the shin, and slipping of the heel from the shin with sudden over-compensatory clonic jerking of the leg as such slipping occurs.

When standing with feet together, the patient with early kuru demonstrates his postural instability with, in addition to his exaggerated tremors, characteristic clawing and gripping movements of the toes which tend to dig into the ground for support. In moderately advanced patients already no longer ambulatory, we have occasionally noted a remarkable sustained patellar clonus elicited by only raising them to partial weight bearing on their own legs; a few ambulatory patients show a shifting, unsustained patellar clonus as they stand trying to maintain balance. Adiadochokinesis is present in early kuru, and "piano playing" and other fine finger movements, rapid clapping and rapid alternating pronation and supination, soon become very awkward and clumsy.

LABORATORY FINDINGS

Laboratory examinations have thus far revealed little departure from normal. Lumbar punctures with check on cerebrospinal fluid (CSF) dynamics and CSF examinations, repeated hematological examinations and urinalyses, numerous clinical chemical determinations and serological studies, have been done on over 85 of our 200 studied kuru cases. These have included 28 studied children under 15 years of age. Hematological studies have regularly included erythrocyte and leucocyte enumerations and differential leucocyte counts from stained thin films,

hemoglobin determinations (Sahli), and Westegren erythrocyte sedimentation rates. Urine analyses have included pH and specific gravity, sugar and albumin determinations and microscopic examinations of urinary sediment and a test for bile. CSF examinations included cell counts and Pandy tests, total protein, sugar and chloride determinations, colloidal gold reactions and Wasserman reactions (both warm and ice-box methods). All of these routine studies have, in general, remained within normal limits with the few exceptions discussed below. In particular, no CSF pleocytosis has been found in any case, even in those near death, and no elevation in CSF protein has been detected. A few cases have given weakly positive luetic serology and luetic-type colloidal gold reactions without associated CSF pleocytosis or protein elevation. We have been unable to interpret these rare aberrant reactions. Spinal fluid pressure and dynamics are normal. Patients tend to have 5% to 10% eosinophilia, occasionally 10% to 20%, but this is apparently not strikingly different from the normal Fore populace. Sedimentation rates are usually normal, although a few elevated sedimentation rates have been encountered, which we could not account for by any detectable intercurrent infection, pregnancy or other cause. The results of liver function tests on over 50 of the patients have been normal, as have blood urea nitrogen determinations.

Serum protein determinations (total serum proteins and serum albumin, total serum globulin, serum gamma globulin) have revealed unusual serum globulin patterns which are, however, characteristic of the serum from many New Guinea highland natives not suffering from kuru. Paper electrophoretic studies of sera and of hemoglobins from our patients have been performed by Dr. Cyril Curtain of the Baker Institute in Melbourne. Enormous elevations of beta globulin in many cases and high alpha globulin levels in some have been encountered. These have been substantiated by electrophoretic studies in the Tiselius apparatus. These findings must be correlated with results on normal Fore natives and this matter is under investigation. Paper electrophoretic study of the hemoglobins from kuru patients has revealed no abnormal hemoglobins.

Auto-immune complement fixation tests (AICF reactions (5)), done using normal human liver, kidney and brain tissue antigens, have failed to reveal any high titer positive reactions.

Blood group testing of over 100 kuru patients for A-B-O, MN-S, C^w, P, Le^a, and F^a and K systems by R.T. Simmons of the Commonwealth Serum Laboratories in Melbourne, has revealed a pattern similar to that reported for natives of Chimbu, Nondugl and Mt. Hagen in the Central Highlands of New Guinea (6,7,8). A smaller number of specimens from kuru patients has been tested for Wt^a (Wright) and Di^a (Diego) groups, and consistent with other results for New Guinea populaces (9), no positive reactions have yet been encountered. Serum titers for anti-A and anti-B were all normal and search for atypical blood group serum antibodies revealed none. At the present time we are conducting with Dr. Simmons extensive blood group genetic surveys of the Fore, Kimi and Keiagana people in the kuru region, in order to compare the results of kuru patients with those for the normal, kuru-free populace. In addition, similar studies are being made on entirely kuru-free Aulana, Yar and Kukukuku populaces surrounding the kuru region.

Serum and total blood copper and manganese levels, along with examinations of other trace metals in blood, urine, CSF and in tissues obtained at autopsy, are being determined. No abnormalities have yet been discovered. In particular, exploratory spectrographic survey of ashed urine and blood samples and of tissues

obtained at autopsy and collected in trace metal-free containers have been carried by A. Walsh and B. Russell to the Chemical Physics Section of the Division of Industrial Chemistry of the CSIRO (Commonwealth Scientific and Industrial Research Organization of Australia). Such qualitative spectrographic analysis should have detected any heavy metal present in significant quantity in the specimens; instead, the analyses indicated the absence of any unusual or toxic metals. Sixteen blood specimens from kuru patients and seven blood specimens from normal Fore control subjects have revealed the following specific elements, with no differences in metal composition between kuru patients and control subjects: iron, magnesium, calcium, sodium, potassium, aluminum and copper. Three kuru bloods showed spectrographic evidence of manganese in addition. Specimens of liver from two kuru subjects and psoas muscle, kidney, bile and spleen have revealed only the same elements with traces of manganese in kidney, spleen and liver, and of zinc in kidney and liver. Eleven urine specimens from kuru patients, seven of which were collected several hours after injection of high doses of BAL (Dimercaprol), have revealed only the same elements present in the blood specimens, while two specimens have also contained traces of manganese. Quantitative atomic absorption analyses for copper in eleven ashed blood samples from kuru cases and six ashed blood specimens from normal Fore control subjects has failed to reveal any significant difference between copper content of blood from control subjects and kuru patients. Similarly, additional blood copper estimations performed by Mr. Baseden and Mr. Southern, soil chemists of the Department of Agriculture in Port Moresby, Papua, have revealed normal or slightly elevated blood copper levels on a number of kuru patients, but no more elevated than such levels on control Fore subjects. Manganese determinations have not yet been completed.

Serological survey for neutralizing antibodies to known encephalitic viruses will later be made on the large serum file of serial serum specimens from our patients which has been accumulated. Thus far, only estimations of neutralizing antibody to Murray Valley encephalitis virus which, with the exception of dengue, is the only arthropod-borne encephalitic virus so far isolated from New Guinea or Papua (10), have been completed. These yielded negative results. They were performed by Dr. S.G. Anderson at the Walter and Eliza Hall Institute in Melbourne, Australia.

Studies on the streptococcal flora in the nasopharynx of kuru patients (in collaboration with Dr. Margaret Holmes of Melbourne), of antistreptolysin titers, of urine amino acids and other biochemical and microbiological investigations are not yet completed and will be reported elsewhere.

PATHOLOGICAL FINDINGS

Ninety of our first 200 studied kuru patients have died during the ten months of our observation, and another dozen are in terminal phases of the disease at present. We have been able to secure complete post mortem examinations on sixteen of these and to remove brain only on an additional two cases. No gross pathological lesions were found, notably, none in the brain, meninges or liver. Histological studies and neurohistological study of the 18 fixed brains are still incomplete and will be reported in a later communication. However, the preliminary pathological study of six cases reveals a widespread neuronal degeneration. The cerebellum and extrapyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives,

thalamus, and pontine nuclei. There is acute destruction of the nerve cells and associated neuronophagia. The lesions are much more diffuse than those found in the slightly similar disease found in Moroccan manganese miners and which in some respects resembles kuru (11). Microscopic study of formaldehyde and Zenkers fluid fixed liver, spleen, kidney, heart, lungs, lymph nodes, pancreas, adrenal, thyroid, testes, ovaries, uterus, bladder, pituitary, stomach, intestine, striated muscle, fascia and bone have revealed no distinctive histological lesions.

Portions of the brain in two cases of kuru obtained within a few hours of death, and placed promptly in buffered glycerine, were shipped by air to Melbourne, where Dr. S.G. Anderson conducted virus isolation attempts at the Walter and Eliza Hall Institute. No infectious agent was isolated from the brain pieces by chorio-allantoic membrane inoculation of chick embryo or by passage intracerebrally in suckling and adult mice.

THERAPY

Patients in all stages of illness, particularly those in the early phases, have been placed on a variety of therapeutic regimens in an attempt to determine whether any of the drugs employed could influence the course of the disease. High doses of sulfadimidine, penicillin, streptomycin, chloramphenicol, and aureomycin have been without effect. High doses of fish liver oil, crude liver extract given parenterally, thiamine, other components of the vitamin B complex, folic acid and many multivitamin preparations and therapeutic doses of ferrous sulfate and ferrous gluconate, have been given without noticeable change in the patient's condition. Other drugs which have been administered in full therapeutic doses for ample clinical trials include acetyl salicylic acid, dl-methionine; the antihistamines--Benadryl (diphenhydramine hydrochloride) and pyribenzamine; the anticonvulsants--phenobarbital, Dilantin sodium (sodium 5-5 diphenyl hydantoinate), and Tridione (3,5, 5-trimethyloxasolidine 2, 4 dione); and hormones--adrenocorticotropin, cortisone acetate, delta-1-hydrocortisone, thyroxin, stilbesterol, testosterone propionate, methyl testosterone, and pregnant mare's serum gonadotropin. The disease has remained unchanged or deterioration had progressed while patients have been on each of these. Intensive courses of BAL in the form of oily injections of dimercaprol, similar to those regimens reported effective in hepatolenticular degeneration, have been used without demonstrable effects on the disease (12-16).

DIFFERENTIAL DIAGNOSIS

Rare cases of recovery which may be due to hysterical mimicry of kuru have been discussed above. The further possibility of formes frustes of the disease has been mentioned. The usual moderately advanced case of kuru offers no diagnostic problem, either to the Fore native or to the physician. Early cases reveal no abnormalities on physical examination other than a slight ataxia and the mildest of tremors. The slight ataxia is often noted by the natives in daily life before we have been able to convince ourselves of its existence, and the mild tremor of the early phase is indistinguishable from that of shivering from cold, fatigue or apprehension. Fatigue or exertion tends to bring out both tremor and ataxia and thus aids in early detection. A convenient test, we have found, is to assess the patient's ability to stand on one foot. In a mild case, in the first month or two of the disease, the patient may be able to maintain equilibrium on one foot with eyes open, but not with eyes closed, while in slightly more advanced cases the patient cannot balance on one foot for

more than a few seconds, even with eyes open.

Clinically, the disease is closely akin to Wilson's hepatolenticular degeneration, but we have found no liver involvement in any of our cases, including sixteen examined at autopsy, and greenish-yellow pigmentation is absent at the sclero-corneal border. The following must all be considered in the differential diagnosis: other heredofamilial neurological degenerations, including the cerebellar and spinal ataxias, such as hereditary spinal and cerebellar ataxia (Friedreich's ataxia), olivocerebellar and olivopontocerebellar atrophy, and parenchymatous cerebellar degeneration and, particularly, heredodegenerative disorders of the corpus striatum involving the basal ganglia, putamen, lenticular nucleus and globus pallidus which include paralysis agitans (Parkinsonism) and Huntington's chorea. None of these other conditions have been seen in these New Guinea natives, other than a congenital tremor of which we have seen three examples, one in a Fore man of about thirty years of age, and the second in a pregnant Kanite woman of about 35 years, and a third in an Aui'ana man of about 45 years of age. These congenital heredofamilial tremors were more regular than those of kuru and unassociated with the profound disturbance of posture and balance or the dysarthria and emotionalism found in kuru; and, of course, they had none of the rapidly progressive degenerative character of kuru. The three natives with these congenital tremors are leading full and essentially normal lives in their native societies. Among the Fore this rather rare congenital illness is embedded in their tradition and is known by the name tavaravain avie (another term for "shivering"), or by the name kogaisa en avie. The latter designation means "possessed by kogaisa". Kogaisa is the name of a tall broad-leaved plant whose leaves tremble in a breeze, in a manner suggestive of the tremors of this affliction. The Fore believe that a pregnant woman who breaks this plant is visited by a "dream man" and subsequently delivers a child suffering from this congenital tremor. The Aui'ana, among whom we have recorded several cases of this type of tremor, call it kogaisantamba.

Sporadic cases of Parkinsonism have been observed at Chimbu, Mount Hagen, Lufa and at Goroka in highland indigenes, but none could be confused with the rapidly progressive and fatal course of kuru.

The still mysterious, etiologically unsolved encephalitis lethargica (Type A encephalitis, von Economo's encephalitis, encephalitis epidemica) epidemic in Europe in the decade following 1916, led to a high incidence of post-encephalitic Parkinsonism and, at times, the antecedent acute encephalitis is said to have produced only very minor clinical manifestations. However, none of the many descriptions of this strange illness (now disappeared), or of the more recent sporadic alleged cases thereof, are consistent with the pattern of disease seen in kuru. Furthermore, none of our brain specimens examined neurohistologically have shown lesions similar to those described for this illness.

PROGNOSIS

Kuru, as discussed above, is usually an inexorably and rather rapidly progressive degenerative disorder of the central nervous system leading to total incapacitation in under one year from its onset in the majority of patients. Early cases without strabismus, slurring or blurring of speech, or complete loss of equilibrium, may remit transiently or recover, or, rarely, periodically remit

between menstrual periods. The problem of whether these rare cases are the same disease or other syndrome has been discussed above. Once the patient is no longer able to walk, death in under a year seems inevitable and no form of therapy which we have used has influenced the outcome.

EPIDEMIOLOGY

The total population of all the villages and hamlets afflicted with kuru is about 16,000, some 11,000 of whom are the Fore people themselves. In this region we have found and studied 200 active cases of kuru since the inauguration of our Kuru Research Project in early March 1957. Of these patients, 90 have already died of kuru. Another dozen cases are near terminal. We have by no means found every case in the region, although we believe we have found most of them. We estimate that some 150 to 175 cases of kuru may currently exist in the region and that 1% of the total population are at present afflicted with the disease and can be expected to die therefrom during the coming year. This is a conservative estimate, since in that portion of the affected population which we have fully surveyed--over two-thirds thereof--somewhat over one percent of the people are currently afflicted with kuru. In certain Fore clans and tribes the present incidence of kuru reaches 5% to 10% of the population, and over 50% of all deaths in some of these communities over the past five years have been from kuru.

The extent of kuru into the linguistic groups surrounding the Fore is illustrated in the accompanying map (Figure 2), in which the kuru region is shown on a much larger scale than in the previous map (Figure 1) locating this area in New Guinea.

Insert Figure 2 here.

The disease is so strikingly clear and so dramatic in its symptomatology and course that valid histories of kuru deaths in the past can easily be obtained. Interrogation of native informants whose reports are verified by independent cross-checking reveals that kuru has been present for at least 25 years. A few well-verified cases are said to have occurred 25 to 35 years ago. Old informants usually add that the illness was not present in their youth, but there is no way of assessing the reliability of such affirmations and we question strongly the validity of this contention. Until the current decade very little attempt to establish government control was exerted, and until this year only two Caucasians have been resident in the entire region at one time. Most clans were first censused by government census patrols between 1951 and 1956. From notes in village census books over the past one to six years, it is thus possible to verify a great many of the reported kuru deaths. In most clans kuru deaths are recalled before the first census patrol appeared. Thus, kuru cannot be associated with the entry into the region of Europeans. However, intertribal trade routes may have introduced certain new crops and occasional manufactured items before European entry.

Age and Sex Incidence: Kuru is predominantly a disease of women. The age and sex distribution of the first 200 cases we have studied since March 15, 1957, is summarized in Table 1.

Insert Table 1 here.

It will be noted that 23 1/2% (i.e. 47) of our 200 cases occur in pre-adolescent or early adolescent children under 15 years of age; the remainder are in older patients. Our youngest patients are two boys, 4 to 5 years of age, and we have recorded no history of a case of kuru in a child under this age. There is a definite decreased incidence in early adolescence and a decided change in sex incidence with age. Of the 47 cases in children, 34 occurred in children under ten years, while only 13 were in children whose age was estimated at 10 to 14 years. All ages are, of course, estimated, since the natives keep no track of age. Accuracy of estimation is increased in childhood and adolescence. At all ages but mid-to-late adolescence (15 to 19 years) there is predominance of cases in females, but among adults who comprise over two-thirds of the cases, there is a most dramatic female preponderance with a male:female ratio of 1:7.8 among patients 20 to 29 years of age, and with only two cases of kuru in men among the 93 cases in patients whose age is estimated at 30 years of age or over. Since over two-thirds of the cases are in adults, the full impact of the disease is upon the young adult and middle-aged woman, and it is evident that kuru has been a major factor in producing the current male preponderance in the Fore population. One might speculate that the Fore pattern of early child marriage for girls--boys do not marry early--has been at least, to some extent, determined by the vulnerability of the childbearing populace to kuru.

ETIOLOGY

The Problem of the Possible Post-Infectious Etiology of Kuru: We have been unable to elicit any consistent history of mild or severe antecedent illness which might be interpreted as an acute infectious disease. No seasonal variation in either time of onset or of death of kuru cases has been detected. Among the Fore and their neighbors there is no tradition nor memory of any epidemic of encephalitic disease. During the ten months of kuru investigation, we have been supervising a regional hospital serving the 30,000 population censused from the Okapa Patrol Post, and during this period we have observed epidemic pertussis, measles, chickenpox and epidemic parotitis. In addition, we have seen epidemic upper respiratory infections, epidemic bronchopneumonia of infants and young children, and epidemic gastroenteritis of infants--these latter three conditions of undetermined etiology--and we have encountered seven cases of acute bacterial meningitis (with identification of N. intracellularis in four, D. pneumoniae in one, and H. influenzae in two).

Furthermore, during the past four months we have seen five cases of benign aseptic meningoencephalitis with transient CSF pleocytosis of from 180 to 1200 cells per mm³, with 80% to 100% of the cells mononuclear. Such patients have been carefully studied. They have been children in all but one instance, which occurred in a young adult female. The illness has more closely resembled benign aseptic (lymphocytic or mononuclear) meningoencephalitis than acute encephalitis, for there have been no ocular symptoms and no somnolence, coma, convulsions, pareses or paralyses, and there has regularly been fever, malaise, irritability, severe anorexia, headache and posterior neck pain and stiffness. All have recovered, although convalescence has been slow and the patients have been ill for over one month before they could resume normal activity. In two instances we have had two patients from the same village simultaneously ill with this syndrome.

The etiology of these cases of meningoencephalitis remains undetermined. They have not been associated with cases of mumps in their villages. No virus

has been isolated from specimens of CSF and of blood taken from three acute cases and sent to Australia under refrigeration for animal and chick embryo inoculation. Acute and convalescent serum pairs have been collected from these five patients for examination for antibodies to those viruses and leptospirae known to produce this syndrome in man. Mumps has in this way been ruled out, but other results are not yet available.

None of our kuru cases present a history of a similar illness antecedent to their kuru, and these five cases of meningoencephalitis have now recovered without sequellae. When these cases were shown to the kinsmen of several kuru patients and to the kuru patients themselves, they all denied that a similar illness had preceded the kuru in the recent or remote past. Leprosy and yaws are less frequent among the Fore than in many surrounding populaces who do not suffer from kuru, and malaria is rare. Thus, we have observed no infectious disease which could readily be suspected as a possible regular antecedent to kuru, although many new cases of kuru are constantly developing during our period of intense medical surveillance of the kuru region. Furthermore, although some one-third of kuru patients do report some headache and knee pains, and occasionally fever, cough and coryza antecedent to the insidiously appearing ataxia (the first signs of kuru), we have not yet actually observed those symptoms in anyone who has progressed to clinical kuru. Therefore, we must reluctantly conclude that kuru is apparently not of post-infectious etiology.

The Problem of the Possible Toxic Etiology of Kuru: Kuru resembles in many respects Wilson's hepatolenticular degeneration, in which research has demonstrated abnormalities in serum ceruloplasmin and copper transport and associated abnormal depositions of copper in the body (18). The neurological manifestations of chronic manganese poisoning (11) and, to a lesser extent, of chronic mercury poisoning, strongly suggest the symptoms of kuru. In view of this, we have made intensive search for possible heavy metal poisoning in our kuru patients. Some of these studies were discussed under the section on Laboratory Findings. In collaboration with Miss Lucy Hamilton, we have made extensive studies of Fore diet, and the composition of soil, food and of ashes from cooking fires and house fires in the kuru region is being investigated. All exposure to toxic agents and a search for possible organic poisons, as well as toxic heavy metals, is in progress. Much further study of foods consumed, including the various fungi, grubs and insects eaten, the ashes used as "salt", and of methods of food preparation is required. Thus far, however, nothing in the Fore diet, body painting, and no unusual pica has yet suggested a source of possible toxicity. We have found no abnormal metal content in blood or serum, CSF, urine or in specimens of tissues obtained at post-mortem examination. We have discovered no differences in the handling of food or other raw materials between our Fore kuru victims and well members of their community, nor between kuru-affected communities and neighboring kuru-free communities. Finally, the therapeutic use of repeated courses of BAL (dimercaprol) therapy in high doses has failed to influence the course of the disease, as has removal of the patients for many months from their native village environment to our kuru hospital, where their diet is supervised and supplemented with tinned meat and unpolished rice.

The Evidence for Probable Genetic Predisposition as a Factor in Kuru Pathogenesis: In spite of complex kinship (19) and frequent child adoptions, a reliable enumeration of the pregnancies of any childbearing woman can be obtained. The Fore are polygamous, but tend to defend the marriage contract vigorously. Thus, assignment of paternity is probably no less certain than in many a literate community. Kuru deaths are found in the family history of well over one-half of our

patients and in the parents or siblings of 46% of the 200 studied cases. In addition, certain families possess a dramatic history of kuru, with several siblings, children of a mother who died of kuru, developing the illness at different times, but each at approximately the same age. Furthermore, we have many instances of the so-called law of anticipation, with the children of an affected parent developing the illness at an earlier age than the parent, although at a different time. In only one instance in our series, however, have a mother and child been ill simultaneously.

Villages and hamlets in the kuru region range in population from a few dozen to several hundred inhabitants, the smaller hamlets predominating. Marriages within a single small group of hamlets have been the rule and marriage with close kinsmen has been preferred (19). Thus, it would be difficult to find "control" families in the center of the kuru region without a high incidence of the disease.

During extensive epidemiological investigations to establish the geographical limits and the pattern of kuru incidence (17), we have patrolled over 1,000 miles on foot to almost every hamlet of the kuru-affected region. On the borders between kuru-affected and non-affected populations, it has been possible to obtain histories of occasional, rare, sporadic cases of kuru--often only a single individual case in a community--developing in otherwise kuru-free populations. These cases have more often than not been in women married into these kuru-free communities from kuru-affected areas. Furthermore, they have often developed kuru in the previously kuru-free region after several months, or even years, of residence outside their home kuru-affected hamlets. In addition, we have now seen two cases of kuru which have developed in men from kuru-affected populaces while they were resident fully outside of the kuru region: one in a Kanite laborer to the Papuan coast who developed his first sign of kuru two months after he started work on a Papuan coastal plantation; the other in a Fore prisoner on roadwork in a region north of the borders of known kuru occurrence. Both men were on rationed diets similar to that shared by all others working with them. We have documented other cases of very early kuru having left entirely the kuru-affected region with only minimal ataxia. Their disease has nevertheless progressed to further neurological deterioration and death. These tend to confirm our observation of relentless progression of kuru in our hospital patients on controlled diet and in those patients brought to the Kainantu Hospital, where they are well outside of the known limits of kuru occurrence. Were it not for the much rarer, but most confusing, examples of a few women from apparently low kuru incidence communities developing kuru after entry into the kuru region through marriage, the genetic basis of the malady would appear fully established.

Another item of evidence strongly suggesting genetic predisposition to kuru lies in the history of the Wana Clan of the Ke'efu-Hogeteru Tribe of Keiagana-speaking natives. This clan, on the border of the kuru region, has experienced sporadic cases of kuru for at least 25 years. It is closely related by marriage ties to other clans of the Ke'efu-Hogeteru tribe, closer to the Fore-Keiagana border in which kuru is even more frequent. About 20 years ago, this clan was expelled by fighting from the Ke'efu region and sought refuge among the Kigupa tribe of Keiagana, a kuru-free populace. The Kigupa people remained hostile to the intruders and did not intermarry with them. During two decades of residence in the Kigupa area, the Wana Clan had several of their women die

of kuru while the surrounding Kigupa people had no kuru at all. Two years ago intertribal fighting now largely at an end, the Wana Clan returned to their traditional lands and the Kigupa Clans have moved back onto the sites occupied by the Wana Clan during their sojourn in Kigupa territory. On this ground the Kigupa natives have not developed kuru, whereas the Wana Clan has continued to experience kuru cases, two new cases having developed among the 200 Wana natives since they returned to their traditional grounds in the Ke'efu kuru-affected region. In addition, kuru has occurred in the past in the Kamano communities of Iababi and Onamuga, well outside of the boundaries of the kuru area. It is of interest that these two Kamano communities are unusual, in that they have had extensive Fore and Keiagana marriage contacts from the kuru region during the period of intertribal warfare and many of their kuru cases can be traced directly to kuru region women who have lived among them.

The etiology of kuru therefore remains obscure. No aspect of nutrition or other feature of Fore culture has yet revealed any clue as to what environmental factors are operating in its pathogenesis. Genetic predisposition is strongly suggested by the type of clinical picture the disease presents, by the unusual age and sex distribution of cases, by high familial incidence in a closely intermarried community, by the phenomenon of anticipation (with cases appearing at an earlier age in the second generation), by occasional genealogies wherein several siblings have died of the disease on reaching approximately the same age, and by the pattern of apparent introduction of kuru through marriage into communities of low kuru incidence on the kuru-non-kuru boundary. The historical episode of the kuru-affected Wana Clan bringing kuru with them into a kuru-free region where they fled for refuge during the period of intertribal fighting, but neither intermarrying with the surrounding kuru-free populace nor leaving kuru behind when they departed, is further evidence for genetic predisposition. Finally, the cases of kuru developing in men and women from the kuru region during residence well outside of this region--in one case as far away and in as different an environment as the Papuan coast--all serve to limit the possibilities of toxic etiology. Thus, any toxic agent would have to be carried with them, either as a cumulative poison stored in some tissues of the body and acquired by asymptomatic exposure long previously, or carried in the form of some toxic substance which they take with them from their home communities--any such substance we have been unable to identify. That they find in the new and strange environment a poison unknown to the local populace, or to modern medicine, seems highly unlikely. Should kuru be a self-perpetuating auto-intoxication resulting from either a genetic defect which makes some ordinarily well tolerated substance in diet or metabolism toxic for the patient, such as tyrosine in phenylpyruvic oligophrenia or copper in hepatolenticular degeneration, it would not be surprising that our current techniques of investigation have thus far failed to explain its pathogenesis. The neuropathology has failed to suggest any autoimmune mechanism, such as are presumed to be active in erythema multiforme exudativum (Stevens-Johnson syndrome), periarteritis nodosum, and multiple sclerosis, although this type of mechanism coupled with genetic predisposition to such auto-aggressive phenomena would be an attractive explanation for the disease. Extensive studies of Fore diet, exposure to possible toxic agents, and search for possible infectious factors is continuing, but thus far, we cannot escape the conclusion that strong genetic factors are operating in kuru pathogenesis, probably in association with as yet undetermined ethnic-environmental variables.

SUMMARY

1. A clinical, pathological and epidemiological study of 200 cases of a new paralysis agitans-like illness occurring in natives of the Fore Linguistic and Cultural group in the Eastern Highlands of New Guinea and in their immediate tribal neighbors who intermarry with them, and which appears to be related to the group of heredofamilial chronic progressive degenerative disorders of the central nervous system is described.

2. The disorder affects principally adult females, but almost one quarter of the cases are in children of both sexes. Rarely, adult males are involved. The disease is generally fatal in 6 to 9 months. The occurrence of mild, remitting forms of the disease is discussed.

3. The illness is apparently restricted to the Fore People, some 11,000 in number, and to only those portions of their tribal neighbors, the Auiana, Usurufa, Kanite, Iate, Keiagana, Kimi and Iagaria who are immediately adjacent to the Fore kuru region, an estimated additional population of 5,000.

4. Preliminary neurohistological examination of 6 of the 18 brains thus far obtained from kuru cases has revealed a widespread neuronal degeneration. The cerebellum and extrapyramidal system are most severely affected. There are also changes in the interior horn cells, inferior olives, thalamus, and pontine nuclei. Gross and microscopic pathological study of other tissues from these 18 cases have thus far shown no specific lesions.

5. Acute meningoencephalitis, with a mononuclear pleocytosis in the CSF, has been discovered in the region, but it has been impossible to establish any relationship between this infection, presumably viral, and kuru.

6. No antecedent encephalitis or meningoencephalitis illness, or any other acute infectious disease, has been identified in the study of kuru, and no nutritional or toxic factor has been incriminated as of possible etiological significance in the disorder. If the degeneration of kuru is a post-infectious phenomenon, the antecedent illness must be so mild or subtle as to escape detection by the natives and ourselves.

7. A congenital, familial tremor which does not greatly interfere with a normal life in native society has been found and is easily differentiated from the rapidly progressive degeneration seen in kuru.

8. Extensive search for toxic factors which might be of etiological significance in kuru, in diet, water, pica, smoke, materials used in body painting and in native salt preparations and medicines, has been unsuccessful. Toxic trace metals have not been found in analyses of tissues from kuru patients. The fact that kuru has developed in natives from the kuru region after their long residence in alien environments with kuru-free populaces far outside of the kuru region limits the toxic possibilities markedly. The possibility of a genetically determined intoxication with substances normally present in diet or metabolism is discussed.

9. Genetic predisposition is strongly suggested and the evidence for it is summarized, but the ethnic-environmental variations that are operating in the pathogenesis of kuru have not yet been determined.

ACKNOWLEDGEMENT

We are deeply indebted to Patrol Officer Jack Baker of the Moke Patrol Post for his administrative assistance and personal cooperation in conducting our Kuru Research Project, and to Dr. William Smythe, Miss Lois Larkin, and Mr. John Berkin for their assistance in various aspects of these studies. We are grateful to the Department of Public Health of the Territory of Papua and New Guinea for their support of this study and to Dr. Joseph E. Smadel of the United States National Institutes of Health for his advice and encouragement.

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AGE AND SEX DISTRIBUTION OF KURU CASES

TYPE OF CASE	5-9 Years		10-14 Years		15-19 Years		20-29 Years		30-39 Years		40 Years		All Ages	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Studied in hospital	7	12	4	5	3	1	5	15	2	17	0	14	21	64
Fully examined in village	5	2	2	2	2	4	0	11	0	27	0	10	9	56
Not fully examined	0	8	0	0	4	2	0	13	0	13	0	10	4	46
Total by sex	12	22	6	7	9	7	5	39	2	57	0	34	34	166
Total both sexes	34		13		16		44		59		34		200	
Male:Female ratio	1:1.83		1:1.17		1:0.78		1:7.8		1:28.5		--		1:4.9	

Kodachrome Slides of Kuru Region, Kuru Hospital and of Kuru Patients

for Article by D.C. Gajdusek and V. Zigas on Kuru

Slides are numbered in upper right corner:

- Slide 1. Awarosa, a large Fore hamlet in the Kuru region which has had five cases of Kuru in the current year in a total population of about 100.
- Slide 2. The Kuru Research Center made of Native materials under construction in the center of the picture. This ward was built in May-June 1957 to replace the small, smoky Native hut which served for the first three months of Kuru study.
- Slide 3. Hospital of the Kuru Research Center at the Okapa Patrol Post (elevation 6,500 feet) showing the long Kuru ward built during the study to house Kuru patients and their guardians.
- Slide 4. The Kuru ward which contains five rooms 12 by 15 feet with a large central fire in each room. This ward proved adequate for housing up to 40 Kuru patients with their guardians, at which time some 100 Natives would be sleeping in the rooms. A group of Kuru patients are standing and sitting on the left side of the picture.
- Slide 5. A group of six Kuru patients outside of Native houses in the Fore village of Paiti in the southern part of the Kuru region. All are females and only one is a child. These six cases occurred in a populace of only 190. The photograph was taken in June 1957; by September 1957 four of the six patients, including the child, had died of the disease.
- Slide 6. A young adolescent girl in an advanced stage of Kuru who has been carried from the low, dark kunai house on the left to which she had already been terminally confined.
- Slide 7. Two Kuru patients, a mother and her son aged about 12 years, the only two simultaneous cases in a parent and child in our series, who are from the Kimi Cultural and Linguistic group on the Fore-Kimi border, where contact and intermarriage between the two groups is common. The mother, no longer able to stand without support, died a few months after this picture was taken, and the son died about four months after his mother's death, some eight months after this picture was taken. The mother's mother was a Fore woman.
- Slide 8. Two women with Kuru from the same Fore hamlet who were still attending to their garden work but unable to walk without support of a stick to which each clings in the picture. Both women died within six months of the time this picture was taken.

- Slide 9. A woman with advanced Kuru still able to stand with support from others. A marked internal strabismus had developed and the patient tended to keep her neck flexed. She died a few months after this picture was taken.
- Slide 10. Five women suffering from Kuru at the Kuru Research Center. All five have died of their disease. The woman on the right, in the third trimester of pregnancy, delivered a normal male infant and nursed him for five months before her death. Her condition remained static during pregnancy and deteriorated rapidly thereafter.
- Slide 11. A woman three months before her death from Kuru, whose head had to be restrained from its coarse tremors for photography. A marked internal strabismus had already developed and she could not stand without support.
- Slide 12. A young boy victim of Kuru in his father's arms. This youngster died of the illness only two months later.
- Slide 13. A young Fore boy with moderately advanced Kuru who could still walk with a very clumsy, weaving and swaying gait and who had marked tremors and peculiar somewhat choreiform movements of his trunk and extremities as he tried to maintain an erect posture with feet wide apart. He survived for six months after this picture was taken.
- Slide 14. The same boy as in Slide 13, showing the marked internal strabismus that had already developed.
- Slide 15. A Kimi boy from a family with extensive Fore intermarriages who was suffering from advanced Kuru from which he died a few months later. He is being supported by his father for morning bath at the Kuru Research Center. The residence for the research team appears in the center background of the picture.
- Slide 16. The same boy as in Slide 15, showing the marked internal strabismus that had already developed and the crouching, sitting posture in which he relied upon auxiliary support from the upper extremities to preserve his balance.
- Slide 17. Eight children suffering from Kuru at the Kuru Hospital. All eight have since died from the disease.
- Slide 18. The youngest of our Kuru patients, a boy of about four years of age who had learned to control his tremors by sitting cuddled in fetal posture in his mother's lap. He died five months after this picture was taken.
- Slide 19. Five Kuru patients, all adult women, at the Kuru Hospital. All five have died since this picture was taken and they are all different patients from those shown in Slide 10.

Slide 20. The feet of a Kuru patient standing. Note the sharply flexed toes digging into the ground to gain purchase for maintaining the erect posture. The toes tended to move so much that a fast shutter speed was required for photography.

TO EDITOR:

These illustrations are the first and only colored illustrations on the subject of Kuru that we have submitted for publication. We realize that we are submitting far more photographic material than your Journal can handle; however, we hope that you will select as liberally from what we have submitted as your publishing policy will permit. Kuru IS a new disease to Western medicine and it is unique and incredible from many points of view. The two preliminary reports listed in the bibliography to this paper are the only publications on this "new" disease in the World literature thus far. For this reason we feel justified in offering you such an extensive photographic record, in the hope that you will be willing to publish much of it. Please preserve and return the Kodachrome negatives to us, both those which you may use and those which you cannot use. My mailing address will be:

D. Carleton Gajdusek, M.D.
c/o Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland, U.S.A.

Okapa Patrol Post, via Kainantu
Eastern Highlands, Territory of
Papua and New Guinea

December 31, 1957

Dr. J.E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland, U.S.A.

Dear Joe:

Enclosed are lists of specimens off today for all sorts of rather essential studies, for which I hope the NIH and NINDB groups interested in kuru can arrange. Enclosed is also a list covering some of the specimens sent in the last two shipments.

The first half of the case records, correspondence files and other kuru records on which all my work and paper writing, and future lab studies of kuru, must be based are now off to you via Qantas. Please check on the arrival of this most important shipment, for without it we are really stalemated. In a few days the second and final half or three-quarters of kuru records--maps, case records, correspondence files, lab results and notebooks and, finally, the epidemiological card file, covering all of kuru epidemiology, will be off to you.

I did two post-mortems between 6 p.m. and midnight yesterday, using the crudest of instruments since I had sent all our instruments out to Kainantu for Vin to have them on hand for autopsy of a patient we have been keeping there "outside of the kuru region". I got full cord, performing a laminectomy from the low lumbar to high thoracic, as well as brain and a full sample of all viscera, as well as some of the peripheral nervous system on both patients. These will eventually be off to you. The fresh, refrigerated, tissue (muscle, liver, spleen and kidney) are off to you today for trace element and other chemical studies. Vin also got, yesterday, the brain and cord on the man who died of kuru in our Kainantu series.

Obviously, hospitalization on controlled kuru region-free diet does not alter the progression of the disease. The man who had just died, in fact, developed his disease on the Papuan coast while there as a plantation laborer, and had progressed to its termination without ever being back inside of the kuru region. What do your "toxicologists" say to that? However, if kuru pathology refuses to fit in with genetic hypotheses, then the NINDB group had best get busy on parasitology and fungal, protozoal, etc. studies with real intensity and, if toxicity still is overwhelmingly the 'first choice', what leads can they give us on an agent exposure to which must be asymptomatic and must be able to precede the first development of symptoms by many months, probably many years? The final possibility, that of some strange toxin found by the patients even when they are far outside the region in which kuru is known to have ever previously occurred, seems very, very remote, since those who develop kuru are all ethnically and originally from the kuru region we have fully demarcated now.

I trust you have received the revised manuscript in press in Klinische Wochenschrift. All illustrations and the manuscript are now in their hands, except for the final figure, a detailed kuru region linguistic group map, which I am now trying to complete. I shall mail it to them shortly. Obviously, however, there is an immense further amount of writing to do on kuru, simply from studies of our records, once I get back. I shall stop by Kuala Lumpur briefly, very briefly, en route home and can collect mail there sometime late in January. Write in care of Bob Traub. Obviously, Joe, if we are forced into the genetic corner with kuru, it remains one of the most challenging matters in world medicine, providing an opportunity for a breakthrough in the fields of progressive neurological disorders, enzyme defect genetics, and in the field of human population genetics, so important in these days of radiation consciousness. Thus, whatever the outcome, kuru looks like a good bet for future study. I shall be anxious to discuss all this with you and others at the NIH shortly in person.

Sincerely,

/s/ Carleton

Okapa Patrol Post
via Kainantu, Eastern Highlands
Territory of Papua and New Guinea
December 24, 1957

Dr. Graeme Robertson
Department of Neurology and Neurosurgery
The Royal Melbourne Hospital
Victoria, Australia

Dear Dr. Robertson,

I am sorry to answer your kind letter of November 21st after such a long delay. Actually, I have been preparing to leave daily and constantly have postponed my departure for new developments. The Adelaide team arrived in the persons of Drs. Donald Simpson and Harry Lander, and I set about to dig up cases for them, to open our records and stacks of data to them, and, especially, to learn from them as they surveyed two dozen of our 200-odd Kuru cases. I have been set right on numerous errors in neurologic interpretation and examination techniques by Donald Simpson and he has been a most stimulating collaborator during the past two weeks. I shall now await the arrival of Prof. Robson and Prof. Cleland from Adelaide and then shall be off. Simpson and Lander are leaving today.

The initial reports on Kuru in the New England Journal of Medicine, and the Medical Journal of Australia, contain many minor errors and mis-statements and a good deal of conjecture on which my opinions have slowly altered or shifted, which are all revised and amplified in a longer and more definitive Kuru contribution off to the German literature. Such inexcusable errors as the appearance of dysphasia for dysphagia in the Australian paper are highly embarrassing, but nothing very major has been altered in our current thinking on Kuru. I shall get reprints of the two publications off to you shortly and the manuscripts of subsequent Kuru publications will be sent to you also. Should you be able to criticise, correct, or comment on any of our work, I shall be most flattered and grateful to you.

Dr. Igor Klatzo of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health in Bethesda, Maryland, has seen a large series of Kuru brains, but he has not yet sent us any definitive reports. Preliminary reports on some of them are briefly summarized in our Australian paper and Dr. Simpson has a copy of the more detailed report on one case, which I have asked him to transmit to you. Furthermore, I shall be back in the U.S. working over the volumes of field notes and field epidemiological studies and the stacks of Kuru clinical records at the NIH within a month or two. From there I shall promptly send to you full pathological reports on all material we have studied and I shall try to collect histological preparations on a large series of cases for your scrutiny as well. Donald Simpson and Harry Lander are taking with them a complete autopsy report and specimens, including full brain and cord, of one of our patients who died during their visit here. This will undoubtedly be the best material obtained in post mortem examination, for Simpson himself did the post with complete cord removal. Since a terminal anterior horn cell damage has gradually become more and more apparent to us in our clinical study of Kuru, and since Donald has been able to give us further clues as to how to demonstrate this, cord pathology obviously becomes even more important.

I am most interested in seeing sections of the three cases you have studied for us. There is no chance of their arriving here before my departure and, thus, I beg that you send them to me in America. I shall go over them there at the same time as I am working over the Kuru records for more definitive Kuru epidemiological and clinical reports. My address for these sections and for future correspondence shall be:

c/o Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland, U.S.A.

Thank you, Dr. Robertson, for your interest in Kuru and your valuable assistance to us. I am sorry that the Moresby office unfortunately mislaid in files your pathology reports, bringing them only to our attention long after their receipt. I am also sorry that when I decided to shift much of the biochemical and other Kuru studies to facilities offered to me in the U.S., you were late in being informed thereof. I had kept many of our Australian collaborators fully informed, but in your case I was unpardonably negligent. I am sorry.

May your holiday season be restful and enjoyable.

Sincerely,

(S)

D. Carleton Gajdusek, M.D.

P.S. In recent months the possibility of an infectious etiology in Kuru has again come often under our consideration. We have absolutely no suggestion of an acute meningoencephalitis process, nor of any acute or chronic febrile disease. However, in view of the epidemiology which makes toxicity most unlikely, unless it be coupled with an inborn error in metabolism--enzymatic defect--we are forced to repeatedly reconsider our findings. Infectious etiology, were it in the form of a Treponeme, Borelia, Leptospira, Rickettsia or, especially, some obscure Protozoan akin to Toxoplasma or Pneumocystis carinii, which long eluded the parasitologists even on close scrutiny of the pathological material, must all be considered--although it is an unlikely suggestion, I realize. However, Kuru is a highly "unlikely" disease. Thus, Dr. Robertson, I suggest with apologies that every thought be given to this wild possibility in examining the histological material.

(S)

Carleton Gajdusek

KURU RESEARCH SPECIMENS FOR STUDY AT NIH AND NINDB, BETHSDA, MARYLAND

BLOOD SPECIMENS:

In 30 ml British-type vacuumatic bleeding venules. Fasting specs. drawn December 31, 1957

ATUNA	F-25	early Kuru
YAYARIMESO	F-28	early Kuru
AKE	M-14	early Kuru--moderately advanced.

AUTOPSY TISSUES FOR TRACE METAL STUDIES AND ANY OTHER CHEMISTRIES POSSIBLE

From Autopsy on night of December 29, 1957 in both cases:

NATA	F-9	SERIBE	F-12
Supraspinatus muscle		Supraspinatus muscle	
Liver		Liver	
Spleen		Spleen	
Kidney		Kidney	

BRAINS, Spinal Cords, Peripheral Nerves and all viscera--all formaldehyde fixed--to follow later.

These tissues kept refrigerated as much as possible since collection.

HAIR FROM KURU PATIENTS AND CONTROL FOR ARSENIC AND OTHER ELEMENT STUDIES

NATA: Hair from December 29 shortly before death from kuru on December 29.

SERIBE: Hair from December 29 shortly before death from kuru on December 29.

AOGA: Hair from December 29--terminal kuru.

ASISI: Hair from December 29--terminal kuru.

AKE: Hair from December 29--early to moderate kuru.

ATUNA: Hair from December 30--early kuru.

YAYARIMESO: Hair from December 30--early kuru.

D.C. GAJDUSEK: Hair from December 29--European in residence 10 months in kuru region-- control.

FINGER NAILS FOR ARSENIC AND OTHER TRACE ELEMENT STUDIES

KEGE'I: Recently "recovered" Kuru--only one month since attack.

24 HOUR URINE COLLECTIONS FROM KURU CASES FOR AMINO ACID, SUGAR, AND
OTHER CHEMICAL AND METAL STUDIES: AND FOR STEROID AND HORMONE ANALYSES

30 ml of 20% HCl added to control bacterial contamination.

1. ATUNA	December 29-30	24 hour vol = 420 ml	F-25 yrs
2. YAYARIMESO	December 29-30	24 hour vol = 320 ml	F-28 yrs

Some recent--DECEMBER 1957--shipments of kuru specimens to NIH

Included in a previous shipment were 30 ml venules containing blood
from following patients:

FOPOTA:	recovered Kuru	Female-adult
ONI:	recovered meningoencephalitis	Female-adult
KAWARA:	Kuru case--advanced	Female-adult
AVI'E:	Kuru case--advanced	Female-adult
TAWASA:	Kuru case--mild, slowly progressive	Female-14 yrs

More recent shipment mailed from Kainantu at end of December:

30 ml British-type vacuumatic venules:

KEGE'I:	"recovered" Kuru only 1 month since attack
AMAKIORA:	relapsed, typical early Kuru now after one previous remission Female-6 yrs
AMETMA:	"recovered" Kuru Female-adult
YAKONA:	"recovered" Kuru Female-adult

10 ml British-type vacuumatic venules:

TETE: Kuru--severe	Female-adult
NOKA(NOGA): Kuru --severe	Female-adult
KASIWARI: Kuru --terminal	Male-adult
SAMA: Kuru --moderate	Female-adult

CEREBROSPINAL FLUIDS IN SPECIAL TRACE-METAL FREE BOTTLES

(McCartney bottles with aluminum tops and rubber stoppers)

WA'ETA: Kuru--terminal	Female-aged
ASISI: Kuru --terminal	Male-11 yrs
NATA: Kuru --terminal	Female-9 yrs

JANUARY 6, 1958
[NIH, BETHESDA, MARYLAND]

GAJDUSEK
OKAPA
KAINANTU
NEW GUINEA

RECORDS MANUSCRIPTS BRAINS RECEIVED LAST WEEK STOP

SMADEL

January 10, 1958
[NIH]

Dear Dr. Masland:

This is concerned with Dr. D. Carleton Gajdusek who is being considered for a position as Visiting Scientist in the National Institute of Neurological Diseases and Blindness for a period of time while he analyzes and prepares for publication the voluminous information he collected on the new disease KURU that he has been studying in New Guinea.

I have known Dr. Gajdusek since early 1952 when he came to work with me at Walter Reed Army Institute for Research. As indicated in the accompanying curriculum vitae and bibliography Dr. Gajdusek has had excellent training and a productive experience. He is one of the unique individuals in medicine who combines the intelligence of a near genius with the adventurous spirit of a Privateer. In addition, he is an indefatigable worker who is dedicated in his efforts in medicine. Over and above this he is an excellent laboratory man and a sufficiently good clinician so that he received his Boards in pediatrics before he came to work with me in 1952.

I have no hesitancy in recommending Dr. Gajdusek to the NINDB as a worthwhile candidate for position of Visiting Scientist in that Institute.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Dr. Richard L. Masland
Assistant Director
National Institute of Neurological Diseases and Blindness
National Institutes of Health
Bethesda 14, Maryland

Enclosures

JES:smh

Kainantu, Eastern Highlands
Territory of Papua and New Guinea
January 12, 1958

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland
U.S.A.

Dear Joe,

I am finally out of Okapa en route home. Prof. Robson and a general practitioner from Port Moresby are in for a remaining two weeks of their one month of study, but instead of bringing in the high powered laboratory we had hoped for, they have arrived only to check family histories for 1 month to calculate out some statistical probabilities of genetic etiology. Actually, we have the very same family tree data in both our case files and in the massive volumes and card files of epidemiological data which I shall shortly be sending to you. However, I have most certainly not had time as yet for analysis of the data. It has been most pleasing, however, to find them getting the very identical family trees which we had recorded in the same communities and, although I knew it, it required some such independent check before anyone would believe our story that the Fore natives were at least as good informants on case anamneses and on family background as are white patients in civilized communities.

Actually, Joe, the "political climate" is rather warm. Thus, Prof. Robson and others have obviously been appointed to urge me to squelch rumors that my work was not strongly and heavily supported by the Australian Territorial Government. They are right. It has been well and strongly supported and Vin Zigas, who has shared every bit of it with me, is fully employed by them and they and their administrative staff have provided funds and support from the very onset for all the drugs, building, etc. etc. that this ambitious project has entailed. However, in the early days I was a most unwanted intrusion into some rather nebulous "research plans" involving perhaps the establishment of a Territorial medical research director's post and rather extreme political pushing "hin und her" in an attempt to maneuver certain candidates into the position. An American working in an obviously "choice" research project, such as kuru almost immediately turned out to be, was a decided "fly in the ointment" and for a matter of some 6 weeks I was all but ordered out of the area--a suggestion I did not accept--and then subjected to a cross-fire from Sir Mac, ex Director of Public Health Gunther--now assistant Administrator--and sundry other "politicos." We only screamed for more collaborators and assistance and got excellent support from Dr. Scragg and the Dept. of Public Health in several successive (3 in all) grants for £100 each

for research expenses and also additional funds for building, for drugs, and the obvious expense of running a precarious "Jeep-lift" into isolated Moke over the rather perilous route. Thus, I can most honestly state that we have been most warmly supported from the start by the PHD. All that clouds the picture and still does to some extent is the warring factions in Australian medical politics. Thus, I see that there is now much talk and disturbed discussion that Adelaide University has crept in where Sir Mac and the Hall group thought they might. In fact, Kuru still needs and could well use a high-powered long-term approach of basic research and no group in Australia has yet been ready to give it that nor does it look possible for a while. The Adelaide group is planning to rush out a few--probably many--reports to get the "Australians" into print on the matter....for some reason Vin Zigas does not seem to count to them as an Australian....and, using largely the cases, case material and data we have made available to them, a series of confirmatory Australian reports are due. However, I doubt much that the attitude expressed in the Australian Medical Journal's editorial to our article is much changed on the continent.

Public Health Department is most concerned about my running off with even my personal correspondence files with you, let alone with my personal field notebooks which no one else in the world could possibly interpret. Vin has an almost complete carbon file of all case records. The immense disorganized, uninterpretable, except by me from my scribbled volumes of field notes, epidemiological file is of no use to anyone but me and is now off en route to you in spite of repeated attempts to get me to duplicate the whole thing--a job of some 2 months organization and another 2 months copying at least, for deposit with them. Since it now appears that a group of would-be degree seekers are already parasitising the case records, etc. for degrees which no one in the world but Vin Zigas should be entitled to receive, I am making no effort to leave full records behind and Vin, now about to depart on a much-needed year of leave with both a ruptured knee cartilage and chronic nervous and physical fatigue undermining his health, will leave in another month or so. After vacationing in Europe he is coming through the USA and will stop in on us at the NIH and I have promised to sit down with him and help him get a thesis out to Sydney University where he can, it appears, get for himself the much cherished and fought-over M.D. qualification without which his career is very much hampered. In the meanwhile, while awaiting his arrival, I shall try to get the epidemiological papers and the definitive papers on case analysis and correlation written.

This, then, Joe, should straighten out the constellation of rumors and cross rumors which keep drifting in to us here. The Territorial government has supported our project--if reluctantly--very well. The fact of our study has enraged and chagrined and convulsed Australian medical circles and various private interests from Canberra, Sydney, Melbourne and Adelaide and, I suspect, Brisbane too, have been drawn in but thus far little has materialized.

The final four Kuru brains will be shipped off to you by Vin after my departure. We obtained them each with complete spinal cord. In several cases thyroid glands are also there and pituitary within sella turcica is with every brain and also a few cm. of cervical cord removed from above. Do not let these get lost in unpacking the brains. We plan to send these final four autopsy specimens off to you very shortly. The visceral tissues on these cases have already been posted or are now being posted. Since we believe we have some real endocrine leads in the disease, we suggest strong concentration on the endocrine glands. Uterus and ovaries and testes are sent with the visceral specimens. Microbiological possibilities still appear unexcluded to us. With patients now developing Kuru far outside the "kuru region" after exodus from it and dying--as one of our recent patients--of typical rapidly progressive disease without ever returning to the Kuru region, latent, earlier acquired infection obviously looks more likely than toxin in spite of the pathological urging to toxic thinking from the NIH. Harry Lander tells us that a few finger nail specimens had high arsenic levels--not all--and I strongly urge that you look into rare earths, arsenic, etc. in the finger nails and hair I have sent you. More will be forthcoming.

The last of the Cine film rolls--undeveloped (developing prepaid) Kodachrome reels Nos. 29 and 30 are now off en route to you and these I urge be quickly developed. I shall also enclose with them a few further rolls of developed 35 mm still black and white film for developing and post-card size printing for the KURU picture file.

Cyril Curtain is receiving my permission to report independently the abnormal serum globulin component he found in normal Fore subjects on his Tiselius moving boundary study of our specimens. The Kuru protein data we shall try to work out once I get back to the U.S.

In the past few days I have made a final tribal and linguistic areas map superimposed upon the kuru region border on an immense scale and the original thereof is off now to the editor of Klinische Wochenschrift for the cartographers of Springer Verlag to redraw into an appropriate figure for our German paper now in press. I think that all that we can possibly say about Kuru has been said in that paper and further publication must await the slow process of detailed analysis of our case records, epidemiological reports, and field notebooks. I am very pleased with the selection of the journal, for, although it will not satisfy the Australian "politicos", it will remove the sting of having it appear in an American journal.

Please, Joe, have your secretary send me a copy of the January AMA Archives of Internal Medicine articles on my AICF test if the papers actually are in that issue (January 1958) as I am told they should be. I have not been able to see the proofs and revisions and corrections for me were handled by Lois and Ian at the Hall Institute with nothing but my letters to go on. I am most

anxious to see the papers, and could receive them in a few weeks at Kuala Lumpur where I plan to call very briefly on Bob Traub and the gang en route home. I shall not, of course, stay there any time as I had previously planned, but interrupt there my forward progress as briefly as possible. I hope to receive first proofs of the German article there as well as anything you wish to send me. I shall be most grateful if you will give me this opportunity of reading my own articles before I get to the wolf-pack in Europe. I really have forgotten what I have said. Furthermore, in paper 2, Ian Mackay and I had an argument about keeping the discussion down to earth instead of constructing ethereal castles of elaborate theorizing as my Hall group collaborators were insisting. I do not know just what has come out. On last compromise I seemed to have won out by firmly insisting on rather cautious discussion documenting our "stolen theories" to ancient German literature instead of directly to the "Burnet-Fenner hypotheses".

Further shipments of our Kuru serum file and of our file of normal sera from all 12 surrounding linguistic and cultural groups will be packed off to you from Melbourne in due course. Please find cold-storage space for them and welcome use of aliquots to anyone who has any "bright ideas" which might throw some light onto our problem.

Again, Joe, accept my thanks for all your help and encouragement.

Finally, enclosed are a number of reprint requests to Vin and myself. Since the NFIP has sent me a note stating that they have sent you their 500 reprints of this article since they are forced to photostat it for their collected reprints, will you please ask someone in your office to mail these out for us. Put some reprints aside for me, if you will.

One of the requests is a letter--enclosed herewith--from M.L. Littman at Mount Sinai Hospital. Please read it. He offers to do mycological histology on pathological materials. I have not yet answered him. Should there be no one as competent at NIH, it might be an excellent idea to send him material which you have on hand.

Finally, please tell the NINDS pathologists that the last autopsy specimen that I shall be sending them--brain and cord on ASISI on whom they already have visceral tissues, peripheral nerves, etc. en route to them--had also his two eyes enucleated. They have been formol saline fixed and Prof. Robson will take them to Adelaide where they have, I am told, an excellent ophthalmological pathologist. Thus, we shall have retinal pathology--and I have sent it out to Adelaide to be done.

Peculiar white spots have been noted on normal retinae as well as on those of Kuru patients. They are pin-point sized, stationary, highly refractile white spots, some occurring, even, over the disc itself. They can be solitary or frequent. They can be in one eye or both, and in some patients are very

numerous. Harry Lander first picked them up, and, once seen, we have been noting them ever since. They are not present in all Kuru patients and they are also found in some non-Kuru normal patients.

Enough for now,

Sincerely,

Carleton

P.S. Please tell the NINDS that we have not lost their cine camera and will send it off to you. The Kukukuku patrol did "bugger" the light meter, but it is, I suspect, fully repairable. These will be sent off shortly.

Lae, New Guinea
January 24, 1968

Dear Joe,

I am off today out of the Australian Territory for Hollandia, Dutch New Guinea, on my way home. I have just flown in from Menyamya where I spent my last week here patrolling, collecting ethnobotanical specimens, collecting blood specimens and studying the kuru-free Kukukuku populations just east of the kuru region. Since the Fore-Kukukuku border is the sharpest kuru-non-kuru discontinuity we know of, I felt this advisable. The Kuks on the border still are at warfare, some cannibalism, and without any government control as yet. In spite of this, we have been long among them, collected blood from them, and studied them, and two of my boys, young lads who have assisted in field expeditions, are from such Kukukuku communities. However, the chance to see the central Kukukuku where government and mission control is now complete was the reason for going into Menyamya. They are the "same" Kukukuku, all right, although there are about Menyamya some five distinct language groups, all of which differ from the "wild" Kuk languages I know of. I have documented these additional linguistic groups, secured all the definitive cartographic, linguistic and ecological data available, sent most of it off by mail to you today for the kuru map file, and made rather extensive medical vocabulary lists among four of the language groups. In addition, I collected 131 blood specimens which are already off, refrigerated, to Melbourne, for blood group genetics and abnormal hemoglobin studies, and the serum from which Lois will ship off to you shortly, if it all arrives in good order.

Obviously, this is a most excellent series to contrast with the kuru region studies, it being from a totally kuru-free population, yet bordering on the kuru region and, thus, potentially one of the large populations "threatened" by kuru. I have all the available population data and estimates also.

One of my pet projects for the future is an intensive anthropological, ethnobotanical, ecological, toxic exposure, etc. (including marriage pattern, etc.) contrast between the kuru-affected Fore and the kuru-free Kukukuku, for here the line of discontinuity is sharpest. In addition, I am prejudiced in favor of the Kuks, liking them extremely, although most others react to their sly, sometimes haughty, sometimes unctuous ways adversely. I am already well under way with such a study, but its completion must await the return field study.

Obviously, I put more hope and stock in the possible results of the further laboratory study of kuru, for I believe that microbiological histology for a possible spirochete, protozoan, fungus, etc. is of utmost importance now, along with a fine tooth comb through the histopathology of all systems, including the CNS, with some preference given to the endocrine system. When that finally fails, as it probably will, yet it must be done, the genetic analysis of our family tree data and peripheral region epidemiology will be required. Here again nothing possibly conclusive can be expected, only such and such probability that the illness is genetically determined, with only such and such reliability of the estimate.

In the last resort, unless we are extremely lucky in the infectious disease approach, I believe we shall be forced to push particularly the study of blood, serum, urine and body tissues for trace elements, toxins, and especially, intermediate metabolites and enzyme systems. This, obviously, requires a different approach to specimen collection than we have usually been using. I hope to be able to push along that line, however, to as far as available specimens will permit, and lay plans for the appropriate field methods in the return field attack.

Vin Zigas, as I told you, will visit us in Bethesda, after his European vacation, arriving there in all probability in September. Vin needs pushing, but unless he writes a thesis on kuru and tries to get the cherished British style M.D., his career here or anywhere in the Australian-British area is not very promising for the future. With others planning the same by full "parasitism" of our records and studies, it is only fair that Vin be the candidate to get the thesis out and I have suggested a complete analysis of the vast clinical data, with an evaluation of the therapeutic trials in a presentation on the clinical picture of kuru and therapeutic regimens tried. Since I shall be doing this preparation anyway for our definitive kuru papers, he can manage it rather easily when he arrives, and since the huge thesis required by the University of Sydney, etc. would require a standard but complete abstracting of all clinical charts, etc. in the appendix, at least, there is plenty for him to work on and do. He hopes to spend a few months in the U.S. working on the thesis. I am enthusiastic about this, for it offers a possibility of plotting out before hand a return field approach and, in addition, planning with Vin for some preliminary arrangements in Okapa where things will have died out into complete inactivity, I believe. I am anxious to help Vin with the thesis. He is on vacation pay and thus can scrape through, for he has a year of leave, but I would like to do all we can to make it possible for him to live a bit less frugally (Australian salaries are not as much as the U.S.) with some study grant for a few months or something of the sort, if we can dig one up.

I shall stop briefly at Kuala Lumpur and then be off again toward the U.S. If, Joe, you can reach me with copies of the AMA Archives of Internal Medicine papers by myself on the AICF test (there should be two, one with Ian Mackay and both in the January issue, I was told) I shall be most grateful.

Lucy Hamilton has received her original Kodachromes, and wants to thank you. I am working here with her, arranging for an intensive last push on the Fore ethnobotany. We have Prof. St. John, Department of Botany, University of Hawaii and world authority on pandanus. I have just brought out a huge collection of the five species of wild pandanus which the Kukukuku eat and am arranging for new specimens of the Fore pandanus to come down here to Lae for him. They are all or most "undescribed species" and he will take time out from his vast Dutch New Guinea and Australian survey of the genus to describe first, our kuru/non-kuru area specimens in order to give us some definitive names to rest our work on. He and Kevin White, a botanist here at the Lae Forestry Department, are helping with a list by world experts everywhere (from Belgium, Greece, Italy and Germany to England, U.S. and Australia) on various genera and New Guinea plant groups, and we are getting the duplicate

collections of Fore ethnobotanical specimens off to the appropriate experts, requesting high priority of new descriptions, since these require new descriptions. A large shipment of pressed plants, all labelled with their appropriate destinations within the U.S., i.e., the Arnold Arboretum at Cambridge (Harvard), the Smithsonian Institution, etc., and with the recipients thereat, will be sent off to you shortly. If someone in the NIH can sort them out and redirect them to appropriate experts in the particular genera or group concerned, all this will be indicated on the shipment and we shall be under way. I send them through the NIH as a 'clearing house', in order that we get the data together once again and get them through 'plant inspection' by the already arranged channels. Prof. St. John tells me that at worst the Dept. of Agriculture may demand that they be fumigated, which will not hurt their use for taxonomic study.

Could you, Joe, ask your secretary to send by air mail some five copies of the NEJM reprints to Vin Zigas in Kainantu; another five to Lucy Hamilton Reid (Box 88, Lae, New Guinea--she has just married and is now Mrs. Reid), another five to me at Kuala Lumpur (c/o the Traubs), and finally, five to Dr. Scragg, Director of Public Health, Port Moresby, Territory of Papua and New Guinea. They have ordered their own copies and some few hundred will be en route by surface mail to Vin and the P.H.D. in Port Moresby, but thus far, no copies are available at all. This will take twenty copies in all. Two hundred copies of the Australian journal reprints will be sent by Zigas to you shortly. Keep a stack aside for me, if you will.

Thank you again for all the encouragement and help, Joe. See you soon.

/s/ Carleton

Hollandia, Netherlands New Guinea
January 28, 1958

Dr. J.E. Smadel, Associate Director
National Institutes of Health
Bethesda, Maryland

Dear Joe,

I am having a fascinating time here in Dutch New Guinea and already I have spotted a half-dozen new problems--some good!! But, Joe, don't get worried, for I am leaving for Borneo in a very few days and from there I head for Kuala Lumpur for only a brief stop there en route home. Kuru remains every moment my major interest. You can see from the enclosures that even here, rushing around the "wildest half" of this "world's wildest island"--and second largest, I am still working and writing and always thinking of Kuru. Enclosed is a copy of a letter Voors had just written to Vin Zigas before I met him. I have discussed with him the suggestions at length. He is sharp. However, he did not know of our two recent cases in men both developing fully outside of the Kuru region and progressing to death without ever going back home or returning to a Kuru region diet. He did not know of our epidemiological data, etc. etc. However, his comment did point out that I had left out a sufficient discussion of the "deficiency" possibility in dealing with pathogenetic possibilities in the *Klinische Wochenschrift* paper now in press, and I have just added this enclosed section to augment the already immense paper. It is important, mostly, for bringing the veterinary literature into better focus, for it is the veterinary people (see Proceedings of the Seventh International Grassland Congress 1956-Wellington, New Zealand) who have really opened and solved many problems in this field. Furthermore, in studying veterinary literature I have come upon the astounding, still somewhat mysterious, but most suggestive work of Lee and others on Phalaris Tuberosa toxicity in cattle which produces a staggers syndrome in sheep which is as close to Kuru as a sheep can get, I suppose. Since it also is in the Australasian part of the world it cannot be ignored. I beg you to get someone to dig up the world literature on this for me, to see if anyone in botany and agriculture can tell us if any of the ethnobotanical specimens in the extensive lists I have sent you are related to Phalaris Tuberosa even remotely--our people do eat grasses, cooked, however, but not always. The Phalaris study is naturally very unlikely in view of our epidemiological data....but so is everything including Kuru. Furthermore, its neuropathology must be looked into if reports are available, for it is too inviting a suggestion. I have stumbled upon it here by accident reading veterinary literature on trace metals and pasture poisonings.

Botanical specimens, some for study at Smithsonian and others for trans-shipment to appropriately designated taxonomic centers in U.S. will be arriving sometime in the next month addressed to you. I have left Kevin White and Lucy

working at Lae getting them ready to send out, and have organized further local collections. Soil specimens for as intensive soil analyses as you can arrange for at Department of Agriculture....including, of course, molybdenum, copper, sulfate, etc. etc. etc. levels will soon be sent to you along with fire ash samples from Kuru houses and control men's houses for similar studies. Metal analyses etc. are especially needed. Hair and nails will be forthcoming along with the three further brains on children on whom we also have complete cords which I left hardening in Kainantu. Vin will ship them to you. Those brains I shipped just before leaving Kainantu should already be with you. From here I am mailing extensive stacks of maps and cartological data along with records and books from Dutch New Guinea containing data on New Guinea ecology which is mighty hard to get. Please file all these in the file for me.

Sorry, Joe, for again having so many requests. I hope that you will pardon my repeated letters of this type. As you know full well, I cannot accept Kuru as a minor problem of a stone age people. It is more than that, and if solved will certainly give to medicine important new leads. Furthermore, it offers the best chance of solution, I still feel, of any of the degenerative disorders of the CNS.

Carleton

74a appendix

THE PROBLEM OF POSSIBLE DIETARY DEFICIENCY UNDERLYING KURU

Extensive study of FORE diet has revealed it to be superior in calories, in variety of foods consumed, and, particularly, in protein intake to that of many other New Guinea communities. No vitamin deficiency is found in Fore diet, there is no endemic goiter in the region, and clinically detectable malnutrition of infants, toddlers, and adults is exceedingly rare for a Melanesian community. No geological change has been noted in passing from Kuru to non-Kuru regions and the geological features of the Kuru region are so varied that it seems unlikely that some trace mineral deficiency such as of copper, manganese, molybdenum, cobalt, zinc, etc. could exist everywhere where Kuru occurs. Furthermore, the peculiar age and sex distribution of cases does not suggest a dietary, particularly not a mineral, deficiency, for exposure to trace elements in water and in soil and fire ash contamination of foods would not be less in men than in women and children. On the contrary, pica for soil and contamination of foods with soil might conceivably be greater in women and children than among adult men (since women and children eat more often out in the gardens), and thus produce a relative excess of some trace mineral in soil without it reaching truly toxic concentrations. Thus, an alternative theory is suggested: It might conceivably be possible that excessive consumption of sulfate, molybdenum or some other trace mineral, for example--still at levels below those producing direct toxicity--by certain individuals of a race all members of which are chronically deficient in some other essential trace metal (copper, for instance) might result in a relative deficiency state. Full elaboration of such a theory of pathogenesis would require further understanding

of the interaction and intermediary metabolism of trace metals in man than we now possess and, it must be added, we have found no epidemiological nor laboratory data to support such a suggestion. However, in view of the interesting interrelations of molybdenum and sulfate in producing copper deficiency in sheep and cattle which veterinary investigators have established (Dick, 1956), it is of interest to continue studies, as we are doing, for search for a possible direct mineral deficiency or an indirectly induced deficiency such as occurs in the molybdenum conditional hypocuprosis of cattle (Neenan, Walsh, and O'Moore, 1956) or the "metabolic copper deficiency" induced by excess of sulfate and molybdenum described by Dick (Dick, 1956) in sheep.

Finally, our cases of Kuru first developing in Kuru-region natives after prolonged residence outside of the Kuru region--one even after several months at a Papuan coastal plantation on a rice and tinned meat diet with other supplements given coastal laborers--and progression of such cases to fatal termination without ever returning to the Kuru region require, if Kuru is the result of a deficiency state, that irreversible central nervous system damage occurs long before even the first subjective awareness of ataxia and that the neuronal degeneration progresses even if the deficient diet is discontinued. Our observation of relentless progression of the illness in our hospital-studied cases on controlled diet further suggests this and makes an uncomplicated deficiency seem very unlikely.

Dick, A.T.

- 1956 The effects of inorganic sulphate on molybdenum and copper metabolism in sheep. Proceedings of the Seventh International Grassland Congress, 368-376.

Neenan, M., Walsh, T. and O'Moore, L.B.

- 1956 Some soil and herbage factors associated with the incidence and treatment of molybdenum conditional hypocuprosis on Irish pastures. Proceedings of the Seventh International Grassland Congress. 345-356. (Wellington, New Zealand).

Animal nutritionists have had extensive experience with trace element poisonings and deficiency states of grazing animals on diverse types of pastures. It is tempting to draw a parallel between the localized pasture syndromes they have described and geographically localized Kuru. One specific pasture poisoning, the toxicity of Phalaris tuberosa, a perennial pasture grass, for sheep in Australia and New Zealand, strongly suggests Kuru. In sheep exposed to a phalaris-dominant pasture a staggers syndrome called "phalaris staggers" is produced and this neuromuscular disorder involving hyperexcitability, tremors, ataxia and incoordination, loss of ability to rise and progressing usually to death is in its clinical picture intriguingly akin to Kuru. It has been found that frequent oral administration of soluble cobalt salts to sheep will completely protect the animals against phalaris staggers even when they are grazed continually on pure stands of phalaris. Parenteral administration of cobalt and oral or parenteral administration of massive doses of vitamin B₁₂--cobalt is an integral part of this molecule--have no effect on either the development or course of phalaris staggers. Our

studies of the grasses eaten by the Fore people as a vegetable and of other plants they consume and our epidemiological investigations of the Kuru pattern, however, have failed to suggest any parallel with this grass poisoning of animals.

Lee, H.T.

- 1956 The toxicity of *Phalaris tuberosa* to sheep and cattle and the preventive role of cobalt. Proceedings of the Seventh International Grassland Congress, Wellington, New Zealand, 387-396.

U.S. Army Medical Research Unit
Institute for Medical Research
Kuala Lumpur, Malaya

February 22, 1958

Dear Joe,

Leaving Kuala Lumpur today, bound for Europe and home...work in the Far East is finished. Here are some films for printing into the Kuru file. They are mostly taken already out of the Okapa area, but, I trust, show some fairly good features of leprosy, and also a good deal of the Dutch New Guinea setting.

I am stopping at Heidelberg to check the proofs of the Kuru article in press in *Klinische Wochenschrift*. The long 35mm film on Kuru clinical features is completed with my sound track and in a note from Professor Eccles of Canberra, I learn that he has been asked to be photographed reading or talking, at least, an "introduction" to the film, which is in the script he sent us embarrassingly laudatory of our work. However, the 'political' pressures worrying the Territorial government, i.e. to disguise the fact that I am American. They trace all of our work to the basic 'discovery' of Kuru by Berndt (which I was first to point out, although Berndt is still confusing Kuru with hysterical mimicry and arguing by mail to me that we are really "not trained" to study it, that he is "Australian", etc., etc.)...all very amusing and inconsequential. However, Eccles is doing a fine piece of work for us and helping on every hand.

You can reach me by air mail via the Editor-in-Chief of *Klinische Wochenschrift* in Heidelberg. This film, two 16mm copies which I had asked for, should be sent to you in a few weeks. The films I have taken and which are on hand there, I shall edit as soon as I get back. The South American serology paper I have completed here and mailed to Nancy for final typing and immediate submission to the editor of *Pediatrics*, where it belongs, in that they have a wide South American audience--Spanish and Interlingua summaries of all the articles--looking for papers on Latin America...the paper is an infant child infectious disease antibody screening. The Middle Eastern papers were sent back to you to hang on to until I get there; they are in such shape that they can be very quickly completed. Please hang on to them for me.

You can reach me in Heidelberg.

Sincerely,

/s/ Carleton

Moscow, USSR
March 27, 1958

Dr. Joseph E. Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland
USA

Dear Joe,

I am going to travel by rail to Leningrad tonight at midnight, after five days in Moscow. I have seen Chumakov and he has been most helpful and friendly and is trying to get for me a few more books that Telford Work, Traub and I myself require. I have dug up many books which we need, in Moscow book stores, and Dr. Zhdanov and Chumakov have helped greatly. Some I have sent on to you via the Embassy and thus, please hang on to any that arrive by this route. Also, Joe, please tell your mail room to direct to your office and save anything that comes addressed to me. I am using NIH as an address, having none other in the U.S. to use until I get there. Please see that my name is on their registry and that nothing gets lost.

Chumakov wants very much the RSSE strain from ticks in Malaya and also the Kyasanur Forest Disease, viruses which Telford Work told me he would give him. He insists that Crimean H. F. is not of the RSSE-Louping Ill-Omsk H.F. complex and says he is sorry none of the strains he has tried to get to the U.S. have survived. He claims he will make a new attempt and wants to wait for new isolates from new cases. Thus, I am suspicious that they do not have the virus going now at all and I hope to find out for sure today. However, Chumakov is straight-forward and says he will make a new attempt to get it to us.

He tells me that he now believes the Uzbekistan and the Crimean H. F. viruses are the same. I hope to find out today exactly where they stand on both of these!

In India, Dr. Pukhner (or Pookhuer) from Chumakov's poliomyelitis show met us at Telford Work's lab and he is in India for another two months, arranging large-scale shipments of Indian monkeys to the USSR. Thus, although there are plenty of monkeys in India, the collecting facilities are already taxed and now, the USSR will be putting heavy new loads on the supply. I know little about the situation, but it may be wise to investigate expansion of Indian collection of monkeys if we also depend on them, for the USSR is there now putting in its bid. There ought to be plenty of monkeys for everyone!

I shall see Smorodintsev in Leningrad and then go to Helsinki, Stockholm, Heidelberg and home and, thus, see you, to get to work on Kuru in late April.

I have seen much--far too much to digest--in these travels, but I shall be in good shape to write papers, analyze data and get laboratory work done.

The Australians have made full-length editions of the Kuru picture I edited and scripted and supervised at Okapa and have dubbed in the necessary "politics"....copies which I requested for myself and the NIH may be arriving. Please keep an eye out for them. Thanks for everything.

Sincerely,

/s/

Carleton

Virus Research Centre
30A Wellesley Road
Post Office Box No. 11
Poona 1, India
20 March 1958

Dear Dr. Smadel:

We are sending herewith, on behalf of Dr. D. Carleton Gajdusek, four lots of 35 mm. negatives which he felt could most safely be sent direct to you since he was travelling from here to Russia. I am sure you will be happy to know of this if you have not already been informed.

Dr. Carleton tendered a request through the Soviet Embassy in Bangkok for a visa and permission to take the air route by Aeroflot, the Russian Airline, from Kabul to Russia. He arrived in India on March 9 and enquired, on March 10, at the Soviet Consulate in Bombay for a reply to his request. None had been received. On March 11 he came to Poona to wait, for a reasonably sufficient time, for a reply to be received from Moscow.

He stayed with us for six days and, on return to Bombay, March 17, found the approval not only of his visa but his route via Kabul and Tashkent, where he expected to disembark, possibly to go on to Novosibirsk and Omsk before reaching Moscow. This, of course, was to look into the hemorrhagic fevers and RSSE work. We saw him off on the plane Tuesday night for Delhi with confirmed reservations through to Tashkent. Nothing has been heard of him since, so I presume he departed from India according to schedule and is now enjoying a long anticipated visit in Russia.

Apparently telegrams from both Chumakov and Smorodintsev received at the Bombay Soviet Consulate were instrumental in expediting not only his visa but also the unusual entry route into Russia. I understand that most others visiting Russia take a Russian plane to somewhere in Western Europe.

We very much enjoyed his stay here. The story of Kuru was a fascinating one, which he shared with our staff. We were particularly interested in quizzing him on his latest review of the Russian literature in regard to hemorrhagic fevers and RSSE virus in Russia.

I have met Carleton sporadically during the past several years and know from previous conversations with him how much he looked forward to visiting Russia, particularly to see the localities where diseases occur, about which he had become the translator from Russian into American literature. He was as excited as a school boy when we helped him make final arrangements on Tuesday.

Carleton thinks a great deal of you and all you have done to support his various activities. I am therefore sure that you will be interested in this

account of his latest accomplishments. He will doubtless have much to tell about his adventures when he finally arrives in Bethesda in a month or so.

We would appreciate knowing whatever other pearls of RSSE and Omsk hemorrhagic fever he may have picked up during his current travels.

With best personal regards,

Sincerely yours,

Telford H. Work, M.D.

Dr. Joseph Smadel
Associate Director
National Institutes of Health
Bethesda, Maryland, USA

Encl. Negatives

cc: Dr. Robert S. Morison

Leningrad, USSR
March 30, 1958

Dear Joe,

I have finished my travels in the USSR and I leave tomorrow for Helsinki, then Stockholm. Chumakov was most helpful in Moscow and I saw his new polio vaccine setup. They are using monkey kidney cells and preparing formalized vaccine, although the Leningrad group is already trying live virus vaccine and has all of Sabin's strains going.

In the RSSE complex, they find severe paralytic type tick encephalitis here in the west, as well as in the Far East, but here the milder diphasic meningoencephalitis is predominant and has practically no associated mortality. Tick-borne, as well as milk-borne, cases of this mild disease occur, right up to Leningrad, and near here a small outbreak of the more serious paralytic disease (tick-borne) has also been seen. The Far-Eastern form has dropped from about 30% mortality to only about 5% in recent years with no explanation available.

I am told that RSSE from either ticks or man, from the mild diphasic meningoencephalitis, gives a different clinical picture in *Macacas rhesus* than does the severe tick-borne encephalitis strain of virus, which is serologically indistinguishable. Furthermore, Omsk hemorrhagic fever produces in *Ondatra* (muskrat?), a hemorrhagic disease which the serologically indistinguishable other strains do not! Here then, is a claimed means of laboratory pathogenic differentiation.

Vaccine for RSSE is made still by formalized mouse brain preparation and chick embryo vaccine lacks adequate antigenicity. They are now working on tissue culture prepared vaccine. Much work on obtaining an avirulent live virus vaccine in Smorodintsev's lab has failed thus far, but they now hope to try mild diphasic meningoencephalitis strains as a starting agent.

Live, apathogenic variant of anthrax is a much used, excellent vaccine; similarly, for tularemia!

In Smorodintsev's lab live virus vaccine for everything is the rage. Flu vaccines (mixed A and B and A₂ and B types) are much used and must be given 4 human passages before they really start working well. They even have a good live avirulent vaccine for Asian flu 1957, and this is good now after 4 human to human intranasal starting passages.

Spray nose ↓

culture in 48-72 hours into eggs (or longer)

↓

harvest eggs

↓

spray subject #2

↓

48-72 hours; subculture in eggs, then man etc.

Data looks good and they are fairly sure of themselves.

A group is working on Sendai (D) and another on influenza C, and another on adenovirus and another on Echo, but nothing astounding is available.

The inclusion bodies in 90% of influenza on direct nasal epithelial smear are specific and impressive and often used to control live virus vaccine studies. They are not seen in common colds, etc., they say. It is a very quick and good clinical test for flu.

I have been well received and the Soviet virologists are very anxious to know of what we are doing and apparently quite willing to show and tell of all their problems and successes.

Crimean and Uzbekistan disease Chumakov believes to be one disease and there have now been outbreaks near Astrakhan and across Transcaucasia and thus it forms a single bond of hemorrhagic fever across southern Russia. It goes well in man (psychiatric patients) and poorly in animals as they really appear to have no lyophilized strains (?). They promise to send a new trial sample as soon as new cases are investigated.

Chumakov claims that the Central European Russian hemorrhagic fever of Yaroslavl and Bulgaria and Hungary are EHF with typical albuminuria, pituitary and renal pathology, and the work of human disease transmission from mite suspensions has been verified, he claims. Thus, he has no doubt that Yaroslavl and Volga Basin EHF is identical to Far Eastern EHF and the human transmission from pools of mites and from blood has been accomplished in Central European Russia.

Finally, the EHF-Yaroslavl-Central European Russian hemorrhagic fever--one complex--is thought to be completely independent serologically of the RSSE-diphasic meningoencephalitis complex and these two are thought to be independent of the Crimean hemorrhagic fever-Astrakhan HF-Uzbekistan-Central Asian HF complexes (all probably one virus with varying virulence) which is a third complex across all of southern Russia.

They are all very interested in the Poona isolation of RSSE by Work-Trapido and want the strain which Work says he will give to them.

It may be premature but the Central European Russian HF kidneys Chumakov showed me looked like EHF! I think one can safely think of 3 bands around half the earth:

- I. EHF-Yaroslavl-Central European Russian Hungarian and ?Scandinavian hemorrhagic fevers.
- II. RSSE-diphasic meningoencephalitis-Louping Ill (including Omsk HF and Kyasanur Forest disease).
- III. Central Asian-Uzbekistan-Astrakhan (Transcaucasian)-Crimean-Bulgarian hemorrhagic fevers.

And this sets a frame of thinking, at any rate, for in each group are all grades of virulence and viscerotropic-neurotropic differentiation.

Previous visitors have probably told you all this....but in case they have not, here it is, for it may help cooperative US-USSR work on the group.

Will be in Helsinki on April 1, in Stockholm on April 3 and home before the end of April.... in need of work in the lab and on the papers. What about the Kuru papers for Lisbon meetings with the motion pictures?

Sincerely,

/s/

Carleton

c/o Schriftleitung
Klinische Wochenschrift
Neuenheimerlandstrasse 24
Heidelberg, Germany

April 14, 1958

Dear Joe,

I have finally finished editing a very satisfying and comprehensive report on Kuru, containing all twelve photographs you sent for me to Klinische Wochenschrift, and a very fine detailed epidemiological map on Kuru distribution, as well as the general Kuru area map localization and a good deal of added information to that contained in the last draft of this Kuru report, which I send you. If all goes well, it will be published in May, at the latest in June. I fly home Wednesday night, arriving in New York on April 17th, in the morning. I shall spend the weekend at home, after a three year absence, and then rush to Bethesda to see you and, I hope, find some chance of signing up for a salary of some sort, for the time being at least. I write, therefore, to let you know at long last of my arrival and of my plans to be in Bethesda at the beginning of next week. I can start on a full-time basis if, as I fervently hope, you can still sign me up on or before May 1, 1958.

I have been with the virus group in Tübingen over the weekend, and before I left Sweden I saw Sven Gard and Svedmyr and went over most of what they are up to. In Helsinki, as well as in Stockholm, I found all I could about the status of RSSE work in both countries. From Leningrad and Moscow I learned a good deal more than I could cram into that brief note I rushed off to you from the USSR. I have sent Telford Work a rather longer summary, since he needs it badly. I can dictate a fairly comprehensive "current status" of a number of virus problems in the Soviet Union as I could learn of them, as soon as I get to Bethesda, but it must be done soon before it all slips from my mind. The Scandinavian group must know soon whether Work's plan to present his RSSE-KFD data at Lisbon involves the presence of others working on the hemorrhagic fever-RSSE problem. For if it does, they may change their plans not to be there and decide again to come. In Moscow, I learned that Chumakov will try to be there; perhaps the others as well.

In Uppsala I found, at the Tiselius Institute, a good deal of extreme interest and importance to us, if the Kuru study is to get into neurological biochemistry, enzymology and metal-binding protein studies. Here in Germany, there is also important liaison, but I shall leave most of it unaccomplished in an attempt to get started on the work of records and genetic analyses, of laboratory and pathological report preparation, and further studies, and, in planning for further studies.

The AMA Archives of Internal Medicine papers I managed to see in the January issue that arrived in Moscow. I am a bit peeved, as I read them, at my own caution. We had plenty of evidence that DNA was at least one of the potent intercellular antigens responsible for the antibodies we were finding, and instead of stressing this I have only mentioned it in passing. The AICF work is another thing I want to discuss with you at length, as it impinges

upon cancer immunity, immune tolerance, as well as on a vast constellation of diseases and surgical transplantation problems.

Finally, I hope you can find a post for me, with time enough to get out as well as the half dozen or more Kuru papers waiting to be prepared, the third AICF paper, all but ready for press, the Uruma virus reports with Schaeffer, Buescher, et al., the Middle Eastern serology and Q fever in childhood work, a revision of the RSSE-hemorrhagic fever study (? perhaps not worth the effort), and reports of other work we have completed in New Guinea. This writing, obviously, is my first problem, although essential experimental work hangs demandingly before me.

Enough for the moment...I see no reason why the current schedule should require change for any unforeseen event; thus, until next week.

Sincerely,

/s/ Carleton

April 3, 1958

Dear Dr. Scragg:

Please forgive the long delay in answering your informative and friendly letter of early February. I had planned to wait until Dr. Gajdusek's return and his instatement here at the NIH before writing you, but he has yet to reach the U.S.A. After leaving your area, he sent occasional messages during his stopovers in Malaya and India. He has now arranged to spend some time in Russia with Chumakov and Smorodintsev, both of whom have done outstanding work on the hemorrhagic fevers, which interest Gajdusek very much. Since you also know Carleton well, you will not be surprised by his numerous delays enroute or his individual capacity to do things which could be arranged only with difficulty through official channels. At any rate, he should be back sometime in the next month or so, and I shall look forward to learning more about his most profitable experience in your area.

I am indeed pleased and honored that you and your group are willing to consider the participation of American scientists in future studies on Kuru. I know that your people and the various Australian groups will continue to push hard for solutions regarding etiology and control of this unique disease. I am equally sure that, as more persons learn about Kuru, they too will become interested and will wish to help with the effort. My own work in Malaya and supervision of several field studies in North Borneo have thoroughly impressed me with the need for choosing with great care those persons who are to participate in field investigations. Furthermore, work with such field parties has shown me the necessity for official clearance and the desirability of active collaborative efforts with the scientists and administrators connected with the local governmental groups. When the occasion arrives for individuals or groups from this country to consider coming to New Guinea, I shall attempt to apply the knowledge acquired in Southeast Asia.

Sincerely yours,

Joseph E. Smadel, M.D.
Associate Director

Dr. R.F.R. Scragg
A/Director of Public Health
Department of Public Health
Port Moresby
Territory of Papua and New Guinea

JES:ddp

TO : Dr. J. Smadel, Associate Director, NIH DATE: July 25, 1958

FROM : D. Carleton Gajdusek, M.D.

SUBJECT: Enclosure--and report of trip to N. Y. and Ala.

Enclosed is a copy of our first report on the pathology of Kuru. The extensive paper on the neuropathology goes off to press today. It will appear in Laboratory Investigation. I hope to be able to go over a prospectus of future studies with you sometime towards the end of August.

I was up to see Saul Krugman at Bellevue--with Tony Morris--on Monday, and it appears that they are interested in the pursuit of herpes-like virus story. Tony obtained serial serum specimens from a large number of additional inoculated cases today, to take back to Tokyo with him, and it appears that Krugman's group will be in an excellent position to follow antibody development against standard herpes strains and Tony's virus serially in all of their subsequent inoculated patients. When they finally get the conjunctival cell lines going, they can also attempt isolation from nose and throat washings. The interesting point in this connection is that they have permission to use as inoculum any virus they may isolate from the children involved in their institutional study, whereas they certainly cannot inoculate virus obtained from some foreign source. Therefore, should another herpes-like agent turn up in the nasal pharynx of their inoculated patients, they would be free to test its pathogenicity in additional children in the same institution. Although far from established, the possibility of a close relationship between herpes-like agents and infectious hepatitis is a most intriguing one. Mrs. Poms is typing up Tony's preliminary report from Proc Soc and when I mail it out later today, I will send you a copy for your files.

In respect to -20° C storage of Kuru specimens and other serological specimens from New Guinea, etc., for both biochemical and serological investigations, I wonder whether you would suggest that I seek semi-temporary (1-2 year) space with Pond or some other department here at NIH or--in preference--seek to obtain our own independent deep-freeze space for the Kuru and other New Guinea projects alone.

Dr. J. Smadel -- Office Memorandum 7/25/58

Incidentally, while I was in Montgomery, Morris Schaeffer's group, working with fluorescent antibodies, had some beautifully stained rickettsiae. They claimed that, as one would expect, specific serological identification is possible by this technique. In addition, a sharp Israeli microbiologist working with Schaeffer and about ready to return to Israel, mentioned that he was hoping to submit to the USPHS a request for a grant to study Brill's disease in Israel, since it is an immense problem there, with the massive immigration from typhus regions. He claimed that the endemicity of Murine Typhus and Epidemic Typhus in Israel could probably be excluded as a complicating factor in metropolitan areas where human ectoparasitic infestation would be exceedingly rare, and I did not learn of any further details of what he proposed to study. He is, however, a well-trained laboratory man.

D. Carleton Gajdusek

Enclosure

TO : Dr. J. Smadel, Deputy Director, NIH

DATE: July 25, 1958

FROM : D. Carleton Gajdusek, M.D.

SUBJECT: Enclosed manuscript

Dear Joe:

Enclosed is a copy of Tony's paper on the Age-16 Virus Isolations.

Mrs. Poms, my secretary, has typed it up and we have submitted it to Dr. Goldfarb, editor of Proc Soc. Five carbon copies have gone off to Tony in Tokyo, along with the original draft. I have two copies on file here and the final carbon copy is enclosed herewith--for you.

Sincerely,

D. Carleton Gajdusek, M.D.

Enclosure

TO : Dr. J. E. Smadel, Assoc. Director, NIH DATE: October 15, 1958

FROM : D. Carleton Gajdusek, M.D., OD, NINDB

SUBJECT: Enclosed reprint

The enclosed is a reprint of the Australian blood group paper which has been long coming out. I am fairly proud of it, since we were able to punch a big hole in the "established" hypothesis that the "pure" Australian aborigines were all free of the gene for Group B.

Our studies of New Britain and Papuan blood groups, and the more recent extensive studies of blood group genetics of the Fore people, several hundred Kuru patients and all the surrounding tribal people are all finished and the papers with Simmons already in first draft. However, reports will be a while in coming out, and their full significance will only be apparent as the genetic factors in Kuru are further unravelled.

I am also enclosing the three auto-immune complement fixation papers which we have had reproduced since there was a vast demand for them and the supply was exhausted. However, it is already apparent that even the reproduced issues will soon be exhausted. Fortunately, the reproduction plates are still on file. I am also returning two old papers Helen Ponish found in the files at Walter Reed.

Enclosures

DCG:mp

TO : Dr. Joseph E. Smadel, Assoc. Director, NIH DATE: November 4, 1958

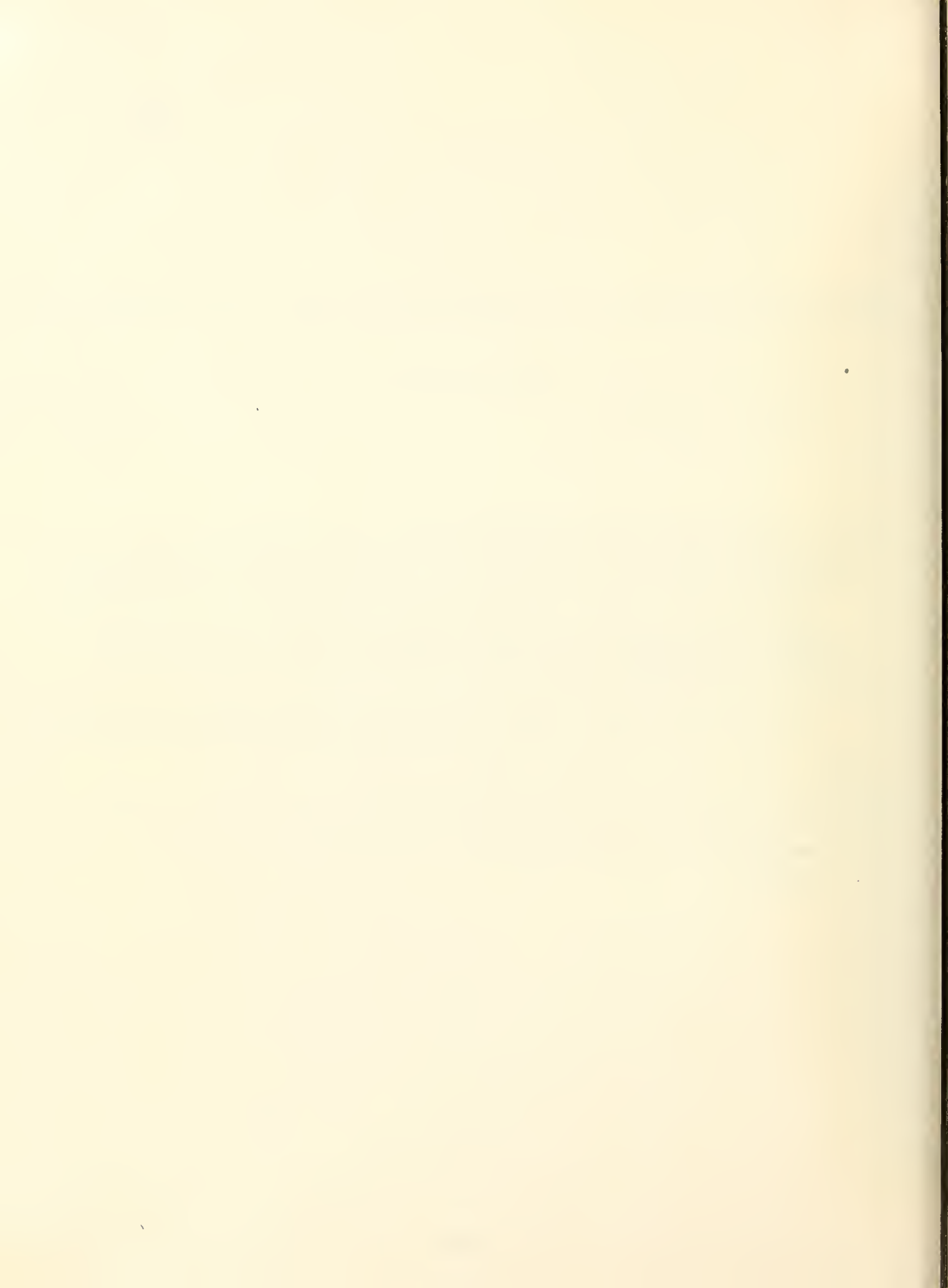
• FROM : Dr. D. Carleton Gajdusek, NINDB, OD

SUBJECT: Attached Letters

The attached are copies of my letters to Dr. R. Scragg and Professor L. Robson. A letter which we have just received from Professor Robson informs Vin Zigas that he will be off to England for six months and plans to go through the United States in March or April. The only Australian worker they have in mind is a medical student who has just graduated, Dr. Auricht, whom both Vin and I know and with whom we can work well. They are restricting their studies and interests, apparently, to further verification of the genetic theories by geneological collections.

The tone of Professor Robson's letter fully implies that he expects us to be back and that Vin will participate in all Kuru investigations, including our own.

Attachments
DCG:mp



Index

Correspondents and Collaborators Cited

<u>Name</u>	<u>Letter number</u>
Abbott, Dr. T. K.	33, 33a
Adams, George	8
Anderson, Dr. S. Gray	9, 11, 12, 14, 14a, 15, 15a, 19a, 23, 29, 29a, 32e, 33a, 38, 42, 49, 49b, 60a, 64a, 64b, 64c, 69b
Auricht, Dr. Clive	82
Bahmanyar, Dr. Mahmud	4a
Bailey, Dr. Pearce	20, 21, 22, 22a, 25, 27, 29a, 40b, 43a, 44, 54, 54a, 62a
Baker, Dr. Carl G.	15a, 30, 32, 32d, 32f, 36, 40b, 46, 52c, 66a
Baker, Patrol Officer Jack	33a, 57, 67, 69b
Baltazard, Dr.	1, 5a
Bankhead, Anne	4a
Barrau, Dr. Jacques	44, 44c
Baseden, Mr.	32e, 69b
Berkin, John	49, 59a, 69b
Berndt, Ronald M.	35a, 59a, 69b, 75
Beyersdorfer, Mrs.	62, 67
Brown, Denny	54, 57
Brown, Dr. Antonio	8
Buescher, Dr. Edward	4, 4a, 13
Burnet, Sir Frank MacFarlane	6, 9, 10, 13, 14, 14a, 15a, 18a, 19, 23, 27, 27a, 27b, 29, 29a, 31, 32a, 32b, 33, 38, 42, 60, 60a, 72
Campbell, Charlotte	7, 8
Cantoni, Dr.	66a
Chumakov, Dr. Mikhail	8, 12, 76, 77, 78a
Cleland, Dr.	68, 69, 70a
Coffey, Charles E.	2a, 5, 6a
Cooper, Dr. G. N.	59a
Cowing, David	29a
Crabill, Dr. R. E.	52a
Curtain, Dr. Cyril	32e, 33, 38, 59a, 59b, 60a, 63, 65, 69b, 72
Danauskis, Joe	13
Dastur, Dr.	40b
Davis, Dr. Perk Lee	64d
Dick, A. T.	74a
DuShane, Dr. Graham	32a, 32c, 32d, 32f
Easeden, Mr.	26a
Eccles, Prof. J. C.	54a, 54b, 57, 69, 75
Edsall, Dr. Geoffrey	2a, 11, 13, 23
Eichenwald, Dr. Heinz	4a
Enders, Dr. John	12, 13
Engel, Dr. King W.	22b

Fairchild, Wilma B.	2b
French, Dr. Eric	9, 10, 11, 12, 15a
Gajdusek, Dr. D. Carleton	all letters and the following supplements: 2a, 2b, 4a, 5a, 6a, 14a, 15a, 16a, 16b, 16c, 18a, 20b, 22a, 26a, 27a, 27b, 29a, 32a, 32b, 32c, 32d, 32e, 32f, 32g, 33a, 37b, 40b, 42a, 43a, 43b, 43c, 43d, 43e, 44b, 44c, 47a, 47b, 49c, 49e, 52a, 54a, 54b, 59a, 59b, 59c, 59d, 60a, 62a, 62b, 63a, 66a, 69a, 69b, 70a, 71a, 76a, 78a
Garland, Dr. Joseph	32a, 37a, 37b, 43d, 43c, 64d
Garry, B.	44b
Gladwin, Dr.	40b
Glass, Bentley	67
Goldfarb, Dr.	80
Goodner, Dr.	1, 5a
Graydon, Dr. John	29a
Greenfield, Dr. Godwin	20, 20a, 21, 25, 62a, 62b, 62c
Gunther, Dr. John	14a, 19a, 33a, 60a, 72
Hamilton, Lucy	33a, 46, 48, 49, 49a, 49d, 49e, 50, 51, 54, 54b, 57, 59, 61, 62, 65, 67, 69b, 73, 74
Hassan, Farag Rizk	1
Haymaker, Dr. Webb	62c
Hicks, Dr.	29a
Hildreth, Dr. E. A.	16a, 16b
Holden, Mr.	26a
Holmes, Dr. Margaret	69b
Horning, Dr. Evan	44, 49e, 51, 52, 52c, 62
Imus, Dr. Henry A.	40b, 43, 43a, 46
Ingalls, Dr. Theodore H.	43d, 43e, 44a, 47b, 49c
Jackson, Betsy	13, 19
Jordan, Dr.	13
Julius, Charles	35b
Kader, Mohamed Abdel	1
Kety, Dr. Seymour	51
Klatzo, Dr. Igor	40, 40a, 40b, 43b, 43c, 43e, 44, 44b, 46, 49, 66a, 70a
Koprowski, Dr. Hilary	16a
Krugman, Saul	79
Kumm, Dr. Henry W.	42a
Kurland, Dr. Leonard	43, 43a, 43b, 46, 52, 52a
Lander, Dr. Harry	68, 69, 72
Larkin, Lois	15a, 29a, 31, 33, 42, 49b, 59a, 59b, 69
Lee, H. T.	74a
Littman, M. L.	72

MacLeod, Dr. Colin	1, 16b
Masland, Dr. Richard	40b, 43a, 62, 63a, 66a, 71a
Mason, Dr.	1
McElroy, William D.	67
Meyer, Capt. Harry M.	3, 4, 4a
Morison, Dr. Robert S.	76a
Morris, Dr. Marion C.	16c, 18, 19, 20b
Morris, Dr. J. Anthony	79, 80
Musgrave, Mr.	49a
Myrianthopoulos, Dr. Ntinios	43b
Ness, Dr.	40, 40b
Palacios, Silvio	8
Papen, Mrs.	44a
Poms, Marion	79, 80
Pond, Dr.	13, 79
Ponish, Helen	81
Pournaki, Dr. Rasoul	4a
Price, Dr. A. V. G.	19a, 26, 26a, 29a, 32e, 33a, 64b
Pukhner, Dr.	76
Rees, A. L. G.	64a, 64b, 64c
Robertson, Dr. Graeme	33, 59c, 60a, 62a, 62b, 62c, 67, 70a
Robson, Prof. H. N.	54, 54b, 57, 68, 70a, 72, 82
Rogers, Nancy	3, 4, 4a, 5, 11, 13, 19, 75
Rivers, Dr. Thomas M.	16c, 18, 18a, 20, 27, 27a, 27b, 29a, 30, 31, 32b, 33, 38, 42, 42a
Russell, B.	64a, 64c, 69b
Sarason, Dr.	40b
Schaeffer, Dr. Morris	4, 4a, 9, 79
Schmidt, Dr. Jack	3, 4, 4a, 6, 8, 11, 12
Schubert, Dr. Bernice	44
Scragg, Dr. R. F. R.	14a, 19a, 33a, 35a, 35b, 54b, 60a, 62a, 62c, 72, 73, 78a, 82
Shy, Dr. Milton	40, 40b, 43c, 43e, 46
Simmons, Dr. Roy	29a, 32e, 33a, 38, 49b, 59a, 59b, 63, 69b, 81
Simpson, Dr. Donald	68, 69, 70a
Smadel, Dr. Elizabeth	13, 19
Smadel, Dr. Joseph E.	all letters and the following supplements: 2a, 2b, 4a, 5a, 6a, 16a, 16c, 18a, 20a, 20b, 22a, 27a, 27b, 32a, 32b, 32c, 32d, 32f, 32g, 37a, 37b, 40b, 42a, 43c, 43d, 44a, 44b, 47b, 49c, 49d, 49e, 52a, 59a, 62a, 63a, 69a, 70a, 71a, 76a, 78a
Smith, Dr. Margaret	7
Smorodintsev, Dr. Anatoli	78a

Smythe, Dr. William	24, 26, 35a, 41, 46, 48, 54, 59b, 69b
Southern, P. J.	26a, 32e, 64a, 64b, 64c, 69b
Stahl, Dr.	2
St. John, Prof.	73
Strome, C. P. A.	1
Sunderland, Prof. Stephen	54, 54b, 57, 69
Symes, Dr.	14a
Taylor, R. M.	1
Traub, Dr. Robert	13, 33a, 70, 73, 76
Underwood, E. J.	35
Vallee, Dr. Bert	66a
Voors, Dr. Antonie	74
Walsh, A.	59b, 64a, 64c, 69b, 74a
Webb, L. J.	57, 62
Wheaton, Zara	59b
White, Kevin	61, 73, 74
Whiting, Dr. Marjorie Grant	43, 43b
Winton, Dr. Ronald R.	47a, 54, 59d
Wipf, Eckart	30, 32f
Wisseman, Dr. Charles	8, 11, 12
Wood, Dr. Ian	14a, 15a, 19a, 29a
Woodward, Dr. Theodore E.	1, 2a, 5a, 6a, 11, 12
Work, Dr. Telford	76, 76a
Wright, Willard	12
Zhdanov, Dr. Victor	76
Zigas, Gloria	57
Zigas, Dr. Vincent	14, 14a, 15, 15a, 17, 19, 19a, 23, 26, 26a, 29a, 31, 32a, 32b, 32c, 32d, 32e, 32f, 33a, 35a, 38, 39, 43e, 45, 47a, 48, 49c, 54, 54a, 54b, 57, 59, 59a, 59c, 59d, 60a, 63, 64, 67, 68, 69, 69b, 70, 72, 82



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